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(57) Abstract

Oligonucleotide sequences encoding gp120 polypeptides from breakthrough isolates of vaccine trials using MN-rgp120 and the encoded gp120 polypeptides are provided. Use of the gp120 polypeptides from one or more of the isolates in a subunit vaccine, usually together with MN-rgp120, can provide protection against HIV strains that are sufficiently different from the vaccine strain (e.g.; MN-rgp120) that the vaccine does not confer protection against those strains. Antibodies induced by the polypeptides are also provided.

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HIV ENVELOPE POLYPEPTIDES AND VACCINE

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to HIV envelope polypeptides and vaccines containing the polypeptides.

Description of the Related Art

Acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus identified as the human immunodeficiency virus (HIV). There have been intense efforts to develop a vaccine that induces a protective immune response based on induction of antibodies or cellular responses. Recent efforts have used subunit vaccines where an HIV protein, rather than attenuated or killed virus, is used as the immunogen in the vaccine for safety reasons. Subunit vaccines generally include gp120, the portion of the HIV envelope protein which is on the surface of the virus.

The HIV envelope protein has been extensively described, and the amino acid and nucleic acid sequences encoding HIV envelope from a number of HIV strains are known (Myers, G. et al., 1992. Human Retroviruses and AIDS. A compilation and analysis of nucleic acid and amino acid sequences. Los Alamos National Laboratory, Los Alamos, New Mexico). The HIV envelope protein is a glycoprotein of about 160 kd (gp160) which is anchored in the membrane bilayer at its carboxyl terminal region. The N-terminal segment, gp120, protrudes into the aqueous environment surrounding the virion and the C-terminal segment, gp41, spans the membrane. Via a host-cell mediated process, gp160 is cleaved to form gp120 and the integral membrane protein gp41. As there is no covalent attachment between gp120 and gp41, free gp120 is sometimes released from the surface of virions and

infected cells.

The gp120 molecule consists of a polypeptide core of 60,000 daltons which is extensively modified by N-linked glycosylation to increase the apparent molecular weight of the molecule to 120,000 daltons. The amino acid sequence of gp120 contains five relatively conserved domains interspersed with five hypervariable domains. The positions of the 18 cysteine residues in the gp120 primary sequence, and the positions of 13 of the approximately 24 N-linked glycosylation sites in the gp120 sequence are common to all gp120 sequences. The hypervariable domains contain extensive amino acid substitutions, insertions and deletions. Sequence variations in these domains result in up to 30% overall sequence variability between gp120 molecules from the various viral isolates. Despite this variation, all gp120 sequences preserve the ability of the virus to bind to the viral receptor CD4 and to interact with gp41 to induce fusion of the viral and host cell membranes.

gp120 has been the object of intensive investigation as a vaccine candidate for subunit vaccines, as the viral protein which is most likely to be accessible to immune attack. At present, clinical trials using gp120 MN strain are underway. However, to date no human vaccine trial has been of sufficient size to confirm or refute vaccine efficacy.

The development of candidate HIV-1 vaccines is burdened by the lack of in vivo or in vitro models of HIV-1 infection that accurately approximate the conditions of natural infection in humans. Several candidate HIV-1 vaccines [Berman et al.; *J. Virol.* **7**:4464-9 (1992); Haigwood et al.; *J. Virol.* **66**:172-82 (1992); Salmon-Ceron et al.; *AIDS Res. and Human Retroviruses* **11**:1479-86 (1995)] have been described that elicit broadly cross-reactive antibodies able to

neutralize a variety of diverse HIV-1 isolates in vitro. However, the relevance of in vitro assays to protective immunity in vivo is uncertain. Although several vaccines have provided chimpanzees with protection from challenge by homologous and heterologous strains of HIV-1, protection has not always correlated with in vitro neutralization assays carried out in T cell lines, or in lectin- and cytokine-activated peripheral blood mononuclear cells (PBMCs) [Berman et al.; *Nature* **345**:622-5 (1990); Bruck et al.; *Vaccine* **12(12)**:1141-8 (1994); El-Amad et al.; *AIDS* **9**:1313-22 (1995); Girard et al.; *J. Virol.* **69**:6239-48 (1995); and Fulz et al; *Science* **256**:1687-1690 (1992)]. While successful protection of chimpanzees is encouraging and has historically proved to be a reliable indicator of vaccine efficacy, the conditions of infection in all experimental models of HIV-1 infection differ significantly from natural infection in humans.

Experimental HIV-1 infection in vivo and in vitro both suffer from the limitation that the in vitro amplification of HIV-1, which is required to prepare virus stocks for in vitro or in vivo infectivity experiments, imposes a genetic selection that results in a spectrum of virus quasi-species that differ from the spectrum of variants present in the clinical specimens used to establish the culture [Kusumi et al.; *J. Virol.* **66**:875 (1992); Meyerhans et al.; *Cell* **58**:901-10 (1989)]. Because of these uncertainties, and even greater uncertainties related to the amount of virus transmitted, the site and cell type involved in initial replication, and the kinetics of virus dissemination, the ability of currently available in vitro or in vivo assays to reliably predict vaccine efficacy is questionable.

One of the candidate HIV-1 vaccines that have

entered human clinical trials is recombinant gp120 prepared in Chinese hamster ovary (CHO) cells from the MN strain of HIV-1 (MN-rgp120) (Berman et al.; *J. Virol.* 7:4464-9 (1992)). To date, approximately 499 adults have participated in Phase 1 and 2 immunogenicity and safety trials of this vaccine. The data collected thus far suggest that MN-rgp120 is safe, immunogenic, and elicits high titers of neutralizing antibodies in greater than 95% of individuals immunized according to a 0, 1, and 6 month immunization schedule [Belshe et al.; *JAMA* **272(6)**:475-80 (1994); McElrath; *Seminars in Cancer Biol.* **6**:1-11 (1995)]. However, during the course of these trials, nine vaccinees who received MN-rgp120 have become infected with HIV-1 through high risk behavior. Small trials, such as these, in populations with low rates of infection and minimally sized placebo control groups do not have sufficient statistical power to confirm or refute vaccine efficacy.

However, effective vaccines based on gp120 or another HIV protein for protection against additional strains of HIV are still being sought to prevent the spread of this disease.

Description of the Background Art

Recombinant subunit vaccines are described in *Berman et al.*, PCT/US91/02250 (published as number WO91/15238 on 17 October 1991). See also, e.g. Hu et al., Nature 328:721-724 (1987) (vaccinia virus-HIV envelope recombinant vaccine); Arthur et al., J. Virol. 63(12): 5046-5053 (1989) (purified gp120); and Berman et al., Proc. Natl. Acad. Sci. USA 85:5200-5204 (1988) (recombinant envelope glycoprotein gp120).

Numerous sequences for gp120 are known. The sequence of gp120 from the IIIB substrain of HIV-1_{LAI}

referred to herein is that determined by Muesing et al., "Nucleic acid structure and expression of the human AIDS/lymphadenopathy retrovirus, *Nature* **313**:450-458 (1985). The sequences of gp120 from the NY-5, Jrcsf, Z6, Z321, and HXB2 strains of HIV-1 are listed by Myers et al., "Human Retroviruses and AIDS; A compilation and analysis of nucleic acid and amino acid sequences," Los Alamos National Laboratory, Los Alamos, New Mexico (1992). The sequence of the Thai isolate A244 is provided by McCutchan et al., "Genetic Variants of HIV-1 in Thailand," AIDS Res. and Human Retroviruses 8:1887-1895 (1992). The MN_{1984} clone is described by Gurgo et al., "Envelope sequences of two new United States HIV-1 isolates," *Virol.* **164**: 531-536 (1988). As used herein, MN, MN-rgp120, the MN clone or isolate refers to MN_{GNE}. The MN_{GNE} amino acid sequence is Sequence ID No. 29.

Each of the above-described references is incorporated herein by reference in its entirety.

Summary of the Invention

Oligonucleotide sequences encoding gp120 polypeptides from breakthrough isolates of vaccine trials using MN-rgp120 and the encoded gp120 polypeptides are provided. Use of the gp120 polypeptides from one or more of the isolates in a subunit vaccine, usually together with MN-rgp120, can provide protection against HIV strains that are sufficiently different from the vaccine strain (e.g.; MN-rgp120) that the vaccine does not confer protection against those strains. Antibodies induced by the polypeptides are also provided.

Brief Description of the Drawings

Figure 1 illustrates the kinetics of antibody response to MN-rgp120 in vaccinees infected with HIV-1.

Sera were collected at the time points indicated and assayed for antibodies reactive with MN-rgp120 (open circles) or a synthetic peptide derived from the V3 domain of MN-rgp120 (closed circles). Arrows indicate dates of injection. Plus sign indicates the first time HIV-1 infection was detected. Shaded area indicates data collected after HIV-1 infection. Data from vaccinee C6 is shown in panel A; C8 in panel B; C7, panel C; C11, panel D; C10, panel E; C17, panel F; and C15, panel G.

Figure 2 illustrates the kinetics of CD4 blocking antibody response in vaccinees infected with HIV-1. Sera were collected at the time points indicated and assayed for antibodies able to block the binding of [^{125}I]-labeled MN-rgp120 to cell surface CD4. Arrows indicate dates of injection. Plus sign indicates the first time HIV-1 infection was detected. Shaded area indicates data collected after HIV-1 infection. Data from vaccinee C6 is shown in panel A; C8 in panel B; C7, panel C; C11, panel D; C10, panel E; C17, panel F; and C15, panel G.

Figure 3 illustrated predicted amino acid sequences of envelope glycoproteins (gp120) from breakthrough viruses. Proviral DNA sequences were amplified by PCR from PBMCs and cloned into the PRK5 expression plasmid. Two clones from each infected vaccinee were sequenced from double stranded plasmid DNA. Sequence numbering is with reference to the initiator methionine residue of gp120. For the purpose of comparison, the sequences shown begin at amino acid 12 of the mature, fully processed, envelope glycoproteins (corresponding to position 41 of the gp120 open reading frame). Shaded areas indicate sequences at neutralizing epitopes, dark boxes indicate polymorphisms thought to be important for the binding of virus neutralizing MAbs reactive with MN-rgp120.

Conserved (C) regions and variable (V) regions are indicated above the sequences. Boxes indicate sequence homologies and polymorphisms.

Figure 4 illustrates immunoprecipitation of recombinant gp120 prepared from breakthrough viruses. Recombinant gp120s from the seven breakthrough viruses were prepared by transient transfection of 293s cells. Cells were metabolically labeled with ^{35}S methionine and growth conditioned cell culture supernatants were immunoprecipitated with polyclonal antisera to MN-rgp120. Immunoprecipitates were resolved by SDS-PAGE and visualized by autoradiography. C8 lanes a and b correspond to clones C8.3 and C8.6; C6 lanes a and b correspond to clones C6.1 and C6.5; C7 lanes a and b correspond to clones C7.2 and C7.10; C17 lanes a and b correspond to C17.1 and C17.3; C11 lanes a and b correspond to clones C11.5 and C11.7; C10 lanes a and b correspond to clones C10.5 and C10.7; C15 lanes a and b correspond to clones C15.2 and C15.3.

Figure 5 illustrates binding of monoclonal antibodies to recombinant gp120 from breakthrough viruses. Growth-conditioned cell culture supernatants were collected from 293s cells transiently transfected with plasmids directing the expression of breakthrough virus envelope glycoproteins. The relative rgp120 concentrations were determined by ELISA using MAb 5B6 specific for the HSV-1 glycoprotein D flag epitope at the amino terminus of all of the rgp120 variants described herein. The resulting rgp120 preparations were captured onto wells of microtiter plates coated with a polyclonal antibody specific for a conserved sequence in the C-terminus of gp120. The binding of virus neutralizing monoclonal antibodies reactive with gp120 was determined by ELISA. A, binding by MAb (5B6) specific for the HSV-1 glycoprotein D flag epitope; B, binding by MAb (1034) against the V3 domain of

MN-rgp120; C binding by MAb (50.1) raised against a synthetic peptide corresponding to the V3 domain of MN-rgp120; D, binding by a human MAb (15e) known to block the binding of gp120 to CD4.

Figure 6 depicts the mature envelope glycoprotein (gp120) from the MN clone of the MN strain of HIV-1 (SEQ. ID. NO. 29). Hypervariable domains are indicated in bold, and the V and C regions are indicated (according to Modrow *et al.*, *J. Virology* **61**(2):570 (1987). Potential glycosylation sites are marked with a (*).

Detailed Description of the Invention

The present invention provides gp120 polypeptides from breakthrough isolates of HIV vaccine trials. Novel oligonucleotide sequences encoding gp120 from breakthrough isolates which can be used to express gp120 are also provided. Use of gp120 polypeptides from one or more of the isolates in a subunit vaccine, usually together with MN-rgp120, can provide protection against HIV strains that are sufficiently different from the vaccine strain (e.g.; MN-rgp120) that the vaccine does not confer protection against those strains.

In one embodiment, the vaccine is based on the use of the MN-rgp120 polypeptide (Sequence ID No. 29) and gp120 polypeptides from MN-like viruses that include neutralizing epitopes that are not present in the initial vaccine strain, and are sufficiently different from those of the vaccine strain, to have been able to cause HIV-1 infections in MN-rgp120 vaccinated individuals (i.e.; to result in breakthrough infections). Use of the initial vaccine strain empirically determines the viruses present in the population that contain additional neutralizing epitopes sufficiently different from those of the

vaccine strain to escape protection induced by the vaccine strain. Use of an initial representative gp120 polypeptide in a vaccine acts as a sieve so that viruses that are not effectively protected against by the vaccine strain breakthrough the vaccine, empirically resulting in determination of additional strains in a given geographic region that are not protected against by the initial vaccine strain. Use of gp120 from those breakthrough isolates complements the vaccine isolate by providing additional neutralizing epitopes not present in the initial vaccine strain, therefore creating a more complete vaccine that confers protection against multiple different virus strains in the region.

Prior HIV-1 vaccine strategies were based on selection of appropriate candidate vaccine polypeptides based on homology alignment studies. However, since some of the neutralizing epitopes are conformation-dependent and the location of all of these epitopes is not known, this approach necessarily cannot determine all of the neutralizing epitopes that should be included in a vaccine for a particular region. In contrast, the present approach uses a selected representative strain and empirically determines strains that are sufficiently different and therefore breakthrough the barrier of protection provided by the initial vaccination program. Those strains can be included in the vaccine to confer more complete protection from HIV strains in the region. In addition, those strains can be used alone to confer protection against the breakthrough virus.

In another embodiment, the invention comprises a vaccine containing a first HIV gp120 polypeptide sequence and a breakthrough isolate HIV gp120 polypeptide sequence from a vaccinee vaccinated with a vaccine including the first HIV gp120 polypeptide

sequence, the HIV gp120 polypeptide sequences being in a suitable carrier. Fragments of one or both HIV gp120 polypeptide sequences can be substituted for one or both of the corresponding HIV gp120 polypeptide sequences.

Preferably, the first gp120 polypeptide sequence contains neutralizing epitopes found in one or more gp120 polypeptides present in isolates from the geographical region where the initial vaccine (i.e., the vaccine that gives rise to the breakthrough isolate) is administered. More preferably, the first gp120 polypeptide sequence contains at least one of the more common neutralizing epitopes for the region, and most preferably the first gp120 polypeptide sequence contains at least one of the three most common neutralizing epitopes.

gp120 polypeptide sequences suitable for use as the first gp120 polypeptide sequence include gp120 MN, the Thai isolate A244 sequence (hereinafter "gp120 A244"), gp120 MN-GNE6 (Sequence ID No. 31; also known in the art as "gp120 GNE6"), and gp120 MN-GNE8 (Sequence ID No. 33; also known in the art as "gp120 GNE8"), and the like. gp120 MN, gp120 MN-GNE6, and gp120 MN-GNE8 are especially preferred for use as the first gp120 polypeptide sequence in initial vaccines for North America. gp120 A244 is especially preferred for use as the first gp120 polypeptide sequence in initial vaccines for Thailand.

In a variation of this embodiment, the vaccine includes two different (i.e., first and second) gp120 polypeptide sequences, or fragments thereof, in combination with a breakthrough isolate HIV gp120 polypeptide sequence. The latter can be from a vaccinee vaccinated with either or both of the first and second HIV gp120 polypeptide sequences.

Exemplary vaccines include those containing

combinations of gp120 MN, gp120 A244, gp120 MN-GNE6 (Sequence ID No. 31), and gp120 MN-GNE8 (Sequence ID No. 33). Combinations of gp120 MN and gp120 A244 or gp120 MN-GNE8 (Sequence ID No. 33) with a breakthrough isolate HIV gp120 polypeptide sequence are especially preferred.

In vaccines containing gp120 MN, the breakthrough isolate HIV gp120 polypeptide sequence can be an HIV gp120 polypeptide sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof.

The term "subunit vaccine" is used herein, as in the art, to refer to a viral vaccine that does not contain virus, but rather contains one or more viral proteins or fragments of viral proteins. As used herein, the term "multivalent", means that the vaccine contains gp120 from at least two HIV isolates having different amino acid sequences.

The term "breakthrough isolate" or "breakthrough virus" is used herein, as in the art, to refer to a virus isolated from a vaccinee.

The terms "amino acid sequence", "polypeptide sequence", and "polypeptide" are used interchangeably herein as in the art, as are the terms "nucleic acid sequence", "nucleotide sequence", and "oligonucleotide".

Polypeptides from Breakthrough Isolates

The gp120 polypeptides of this invention correspond to the amino acid sequences of seven breakthrough isolates which are illustrated below in Table 1. A polypeptide of this invention includes an HIV gp120 amino acid sequence illustrated in Table 1 (Sequence ID Nos. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27) and fragments thereof. The polypeptides of this invention can include fused

sequences from two or more HIV gp120 or gp160 amino acid sequences.

The polypeptide can also be joined to another viral protein, such as a flag epitope amino acid sequence. The term "flag epitope" is used herein, as in the art, to denote an amino acid sequence that includes an epitope recognized by a monoclonal antibody. Flag epitopes facilitate using single monoclonal antibody affinity purification of a plurality of different recombinant proteins, each having the flag epitope recognized by the monoclonal antibody. Numerous amino acid sequences can function as flag epitopes. The N-terminal sequences of Herpes Simplex Virus Type 1 (HSV-1) glycoprotein D (gD-1) is conveniently used as the flag epitope and its use is described in detail in the examples. The flag epitope is conveniently fused to the N terminus of the HIV gp120 polypeptide sequence. Alternatively, however, monoclonal antibodies that recognize neutralizing epitopes in the rgp120 sequences can be used to affinity purify the amino acid sequences, and a flag epitope can be omitted.

In addition, various signal sequences can be joined to a polypeptide of this invention. Although rgp120 is secreted to some extent in HIV cultures, the amount of the envelope glycoprotein released from (secreted by) the host cells varies widely from strain to strain. Various signal sequences can be introduced into the polypeptide by joining a nucleotide sequence encoding the signal sequence to the nucleotide sequence encoding the rgp120 to facilitate secretion of rgp120 from the cells. For example, Chiron HIV gp120 polypeptides include a signal sequence from tissue plasminogen activator (TPA) that provides good secretion of rgp120. Additional signal sequences are well known and include the N-terminal domain of murine

leukemia virus surface protein gp70 described by Kayman et al., *J. Virol.* **68**:400-410 (1984).

Table 1 illustrates the nucleotide and deduced amino acid sequences for two clones of each the seven breakthrough isolates of this invention. The clones are: C6.1; C6.5; C8.3; C8.6; C15.2; C15.3; C7.2; C7.10; C11.5; C11.7; C10.5; C10.7; C17.1; and C17.3. These sequences are SEQ. ID. NOs. 1-28, the first sequence number for each clone being the nucleotide sequence and the second being the amino acid sequence. The amino acid sequence for MN and the nucleotide and deduced amino acid sequences for MN-GNE6 and MN-GNE8 are illustrated in the sequence listing hereinafter. In the listing for MN-GNE6, a stop codon appears at amino acid residue position 51. This stop codon can be replaced with a codon encoding the corresponding amino acid from MN or MN-GNE8 or another isolate.

TABLE 1

CLONE C6.1

```
                GGG GTA CCT GTG TGG AAG GAA GCA ACC ACC ACT CTA 36
                Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
                  1               5                  10
TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
          15                  20                  25
CAT AAT GTT TGG GCC ACA CAT GCT TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
                    30                  35
CCA AAC CCA CAA GAA ATG GTA TTG GAA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Met Val Leu Glu Asn Val Thr Glu
     40                  45                  50
GAT TTT AAC ATG TGG AAA AAT GAC ATG GTA GAA CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Asp Met Val Glu Gln Met
               55                  60
CAT GAG GAT ATA ATC AGT TTA TGG GAT CAA AGC CTA AAA 231
His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys
 65                  70                  75
CCA TGT GTA AAA TTA ACC CCA CTC TGT ATT ACT TTA AAT 270
Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
          80                  85                  90
TGC ACC AAT TGG AAG AAG AAT GAT ACT AAA ACT AAT AGT 309
Cys Thr Asn Trp Lys Lys Asn Asp Thr Lys Thr Asn Ser
                95                  100
AGT AGT ACT ACA ACT AAT AAT AGT AGT GCT ACA GCT AAT 348
Ser Ser Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn
     105                 110                 115
AGT AGT AGT ACT ACA ACT AAT AGT AGT TGG GGA GAG ATA 387
Ser Ser Ser Thr Thr Thr Asn Ser Ser Trp Gly Glu Ile
               120                 125
AAG GAG GGA GAA ATA AAG AAC TGC TCT TTC AAT ATC ACC 426
Lys Glu Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr
130                 135                 140
ACA AGC ATA AGA GAC AAG GTG AAG AAA GAA TAT GCA CTT 465
Thr Ser Ile Arg Asp Lys Val Lys Lys Glu Tyr Ala Leu
          145                 150                 155
TTT TAT AGC CTT GAT GTA GTA CCA ATA GAA AAT GAT AAT 504
Phe Tyr Ser Leu Asp Val Val Pro Ile Glu Asn Asp Asn
                160                 165
ACT AGC TAT AGG TTG AGA AGT TGT AAC ACC TCA GTC ATT 543
Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val Ile
     170                 175                 180
ACA CAA GCC TGT CCA AAG GTA ACT TTT GAG CCA ATT CCC 582
Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro
               185                 190
ATA CAT TAT TGT ACC CCG GCT GGT TTT GCG ATT CTG AAG 621
Ile His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys
195                 200                 205
TGT AGA GAT AAA AAG TTC AAT GGA ACA GGA CCA TGC AAA 660
Cys Arg Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys
          210                 215                 220
AAT GTT AGC ACA GTA CAA TGT GCA CAT GGA ATT AAG CCA 699
Asn Val Ser Thr Val Gln Cys Ala His Gly Ile Lys Pro
                225                 230
GTA GTG TCA ACT CAA CTG CTG TTA AAT GGC AGC CTA GCA 738
Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
     235                 240                 245
GAA GAA GAG GTA ATA ATT AGA TCT GCC AAT TTC TCA AAC 777
Glu Glu Glu Val Ile Ile Arg Ser Ala Asn Phe Ser Asn
               250                 255
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AAT GCT AAA ATC ATA ATA GTA CAG TTG AGG GAA CCT GTA 815
Asn Ala Lys Ile Ile Ile Val Gln Leu Arg Glu Pro Val
260                 265                 270
GAA ATT AAT TGT ACA AGA CCC AGC AAC AAT ACA ATA AAA 855
Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
        275                 280                 285
GGT ATA CAC ATA GGA CCA GGG AGA GCA TTT TAT GCA ACA 894
Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr
                290                 295
GGA GAC ATA CGA GGA GAT ATA AGA CAA GCA CAT TGT AAC 933
Gly Asp Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn
    300                 305                 310
ATT AGT GGA GCA AAA TGG AAT AAC ACT TTA AAG AAG GTA 972
Ile Ser Gly Ala Lys Trp Asn Asn Thr Leu Lys Lys Val
        315                 320
GTT AAA AAA TTA AAA GAA CAA TTT CCA AAT AAA ACA ATA 1011
 Val Lys Lys Leu Lys Glu Gln Phe Pro Asn Lys Thr Ile
 325                 330                 335
GTC TTT AAC CAT TCC TCA GGA GGG GAC CCA GAA ATT GTA 1050
Val Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val
        340                 345                 350
ATG CAC AGT TTT AAT TGT CAA GGG GAA TTT TTC TAC TGT 1089
Met His Ser Phe Asn Cys Gln Gly Glu Phe Phe Tyr Cys
                355                 360
AAT ACA ACA AAG CTG TTT AAT AGT ACT TGG AAT GAT ACT 1128
Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp Thr
    365                 370                 375
ACA GAG TCA AAT AAC AAT GAT AGT ACT ATT ACA CTC CCA 1167
Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro
        380                 385
TGC AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA ATA 1206
Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Ile
390                 395                 400
GGA AAA GCA ATG TAT GCC CCT CCC ACC AGA GGA GAA ATT 1245
Gly Lys Ala Met Tyr Ala Pro Pro Thr Arg Gly Glu Ile
        405                 410                 415
AAA TGT TCA TCA AAT ATT ACA GGA CTA CTG TTA ATA AGA 1284
Lys Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Ile Arg
                420                 425
GAT GGT GGT ATT AAC ACT AGC GAT GCC ACC GAG ACC TTC 1323
Asp Gly Gly Ile Asn Thr Ser Asp Ala Thr Glu Thr Phe
    430                 435                 440
AGA CCG GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT 1362
Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser
        445                 450
GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA 1401
Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
455                 460                 465
GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG 1440
Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
        470                 475                 480
AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT 1479
Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu
                485                 490
GGG TTC TTA GGA GCA TAA AGC TTC 1503
Gly Phe Leu Gly Ala Xaa Ser Phe
    495                 500 501
```

CLONE C6.5

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    GGG GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA 36
    Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
      1               5                  10
TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
        15                  20                  25
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     CAT AAT GTT TGG GCC ACA CAT GCT TGT GTA CCC ACA GAC 114
     His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
                    30                  35
     CCA AAC CCA CAA GAA ATG GTA TTG GAA AAT GTG ACA GAA 153
 5   Pro Asn Pro Gln Glu Met Val Leu Glu Asn Val Thr Glu
       40                  45                  50
     GAT TTT AAC ATG TGG AAA AAT GAC ATG GTA GAA CAG ATG 192
     Asp Phe Asn Met Trp Lys Asn Asp Met Val Glu Gln Met
                55                  60
10   CAT GAG ANT ATA ATC AGT TTA TGG GAT CAA AGC CTA AAA 231
     His Glu Xaa Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys
      65                  70                  75
     CCA TGT GTA AAA TTA ACC CCA CTC TGT ATT ACT TTA AAT 270
     Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
15         80                  85                  90
     TGC ACC AAT TGG AAG GAG AAT GAT ACT AAA ACT AAT AGT 309
     Cys Thr Asn Trp Lys Glu Asn Asp Thr Lys Thr Asn Ser
                    95                  100
     AGT AGT ACT ACA ACT AAT AAT AGT AGT GCT ACA GCT AAT 348
20   Ser Ser Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn
       105                 110                 115
     AGT AGT AGT ACT ACA ACT AAT AGT AGT TGG GGA GAG ATA 387
     Ser Ser Ser Thr Thr Thr Asn Ser Ser Trp Gly Glu Ile
                120                 125
25   AAG GAG GGA GAA ATA AAG AAC TGC TCT TTC AAT ATC ACC 426
     Lys Glu Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr
     130                 135                 140
     ACA GGC ATA AGA GAC AAG GTG AAG AAA GAA TAT GCA CTT 465
     Thr Gly Ile Arg Asp Lys Val Lys Lys Glu Tyr Ala Leu
30         145                 150                 155
     TTT TAT AGC CTT GAT GTA GTA CCA ATA GAA AAT GAT AAT 504
     Phe Tyr Ser Leu Asp Val Val Pro Ile Glu Asn Asp Asn
                    160                 165
     ACT AGC TAT AGG TTG AGA AGT TGT AAC ACC TCA GTC ATT 543
35   Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val Ile
       170                 175                 180
     ACA CAA GCC TGT CCA AAG GTA ACT TTT GAG CCA ATT CCC 582
     Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro
                185                 190
40   ATA CAT TAT TGT ACC CCG GCT GGT TTT GCG ATT CTG AAG 621
     Ile His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys
     195                 200                 205
     TGT AAA GAT AAA AAG TTC AAT GGA ACA GGA CCA TGC AAA 660
     Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys
45         210                 215                 220
     AAT GTT AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG CCA 699
     Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys Pro
                    225                 230
     GTA GTG TCA ACT CAA CTG CTG TTA AAT GGC AGC CTA GCA 738
50   Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
       235                 240                 245
     GAA GAA GAG GTA ATA ATT AGA TCT GCC AAT TTC TCA AAC 777
     Glu Glu Glu Val Ile Ile Arg Ser Ala Asn Phe Ser Asn
                250                 255
55   AAT GCT AAA ATC ATA ATA GTA CAG TTG AAG GAA CCT GTA 816
     Asn Ala Lys Ile Ile Ile Val Gln Leu Lys Glu Pro Val
     260                 265                 27
     GAA ATT AAT TGT ACA AGA CCC AGC AAC AAT ACA ATA AAA 855
     Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
60         275                 280                 285
     GGT ATA CAC ATA GGA CCA GGG AGA GCA TTT TAT GCA ACA 894
     Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr
                    290                 295
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GGA GAC ATA CGA GGA GAT ATA AGA CAA GCA CAT TGT AAC 933
Gly Asp Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn
    300                 305                 310
ATT AGT GGA GCA AAA TGG AAT AAC ACT TTA AAG AAG GTA 972
Ile Ser Gly Ala Lys Trp Asn Asn Thr Leu Lys Lys Val
            315                 320
GTT ATA AAA TTA AAA GAA CAA TTT CCA AAT AAA ACA ATA 1011
Val Ile Lys Leu Lys Glu Gln Phe Pro Asn Lys Thr Ile
325                 330                 335
GTC TTT AAC CAT TCC TCA GGA GGG GAC CCA GAA ATT GTA 1050
Val Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val
        340                 345                 350
ATG CAC AGT TTT AAT TGT CAA GGG GAA TTT TTC TAC TGT 1089
Met His Ser Phe Asn Cys Gln Gly Glu Phe Phe Tyr Cys
            355                 360
AAT ACA ACG AAG CTG TTT AAT AGT ACT TGG AAT GAT ACT 1128
Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp Thr
    365                 370                 375
ACA GAG TCA AAT AAC AAT GAT AGT ACT ATT ACA CTC CCA 1167
Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro
        380                 385
TGC AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA 1206
Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val
390                 395                 400
GGA AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA GAA ATT 1245
Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile
            405                 410                 415
AAA TGT TCA TCA AAT ATT ACA GGA CTA CTG TTA ACA AGA 1284
Lys Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg
            420                 425
GAT GGT GGT ATT AAC ACT AGC GAT GCC ACC GAG ACC TTC 1323
Asp Gly Gly Ile Asn Thr Ser Asp Ala Thr Glu Thr Phe
    430                 435                 440
AGA CCG GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT 1362
Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser
        445                 450
GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA 1401
Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
455                 460                 465
GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG 1440
Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
            470                 475                 480
AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT 1479
Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu
            485                 490
GGG TTC TTG GGA GCA TAA AGC TTC 1503
Gly Phe Leu Gly Ala Xaa Ser Phe
    495                 500 501
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CLONE C8.3

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G   GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
    Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
      1                 5                  10
TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His
          15                  20                  25
AAT GTT TGG GCT ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
              30                  35
AAC CCA CAA GAA GTA GTA TTG GAA AAT GTA ACA GAA AAT 154
Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn
    40                  45                  50
TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
        55                  60
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GAG GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA AAG CCA 232
Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
 65                  70                  75
TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
            80                  85                  90
ACT AAT TTG GAG AAT GCT AAT AAT ACC GAG AAT GCT AAT 310
Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn
                95                 100
AAT ACC AAT AAT TAT ACC TTG GGG ATG GAG AGA GGT GAA 349
Asn Thr Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu
    105                 110                 115
ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC TTA AGA 388
Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Leu Arg
            120                 125
GAT AAG GTG AAA AAA GAA TAT GCA TTG TTT TAT AAA CTT 427
Asp Lys Val Lys Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
130                 135                 140
GAT GTA GTA CAA ATA GAT AAT AGT ACC AAC TAT AGG CTG 466
Asp Val Val Gln Ile Asp Asn Ser Thr Asn Tyr Arg Leu
        145                 150                 155
ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
                160                 165
AAG GTA TCC TTT GAG CTA ATT CCC ATA CAT TAT TGT GCC 544
Lys Val Ser Phe Glu Leu Ile Pro Ile His Tyr Cys Ala
    170                 175                 180
CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG AAG 583
Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys
            185                 190
TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGC ACA GTA 622
Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val
195                 200                 205
CAA TGT ACA CAT GGA ATT AGA CCA GTA GTA TCA ACT CAA 661
Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
        210                 215                 220
CTA CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG ATA GTA 700
Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Ile Val
                225                 230
ATT AGA TCT GAA AAT ATC ACA GAC AAT GCT AAA ACC ATA 739
Ile Arg Ser Glu Asn Ile Thr Asp Asn Ala Lys Thr Ile
    235                 240                 245
ATA GTG CAG CTA AAT GAA TCT ATA GTG ATT AAT TGT ACA 778
Ile Val Gln Leu Asn Glu Ser Ile Val Ile Asn Cys Thr
            250                 255
AGA CCC AAT AAC AAC ACA AGA AAA AGT ATA AAT ATA GGA 817
Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn Ile Gly
260                 265                 270
CCA GGG AGA GCA TTC TAT ACA ACA GGA GAC ATA ATA GGA 856
Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
        275                 280                 285
GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AAA ACA CAA 895
Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln
                290                 295
TGG GAA AAA ACG TTA AGA CAG ATA GCT ATA AAA TTA GAA 934
Trp Glu Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu
    300                 305                 310
GAA AAA TTT AAG AAT AAA ACA ATA GCC TTT AAT AAA TCC 973
Glu Lys Phe Lys Asn Lys Thr Ile Ala Phe Asn Lys Ser
            315                 320
TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT 1012
Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn
325                 330                 335
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TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA AAA CTG 1051
Cys Gly Gly Glu Ph  Phe Tyr Cys Asn Thr Thr Lys Leu
        340                 345                 350
TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn
                355                 360
ACC GGG AAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
Thr Gly Asn Arg Thr Glu Glu Leu Asn Ile Thr Leu Pro
    365                 370                 375
TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val
            380                 385
GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile
390                 395                 400
AGA TGT TCA TCA AAT ATT ACA GGG CTA CTA TTA ACA AGA 1246
Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg
        405                 410                 415
GAT GGT GGA AGT AAC ACC GGT GAC AAC AGG ACT GAG ACC 1285
Asp Gly Gly Ser Asn Thr Gly Asp Asn Arg Thr Glu Thr
            420                 425
TTT AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA 1324
Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg
    430                 435                 440
AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro
            445                 450
TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTG GTG 1402
Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val
455                 460                 465
CAA AGA GAA AAA AGA GCA GTG GGG ATA GGA GCT ATG TTC 1441
Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
        470                 475                 480
CTT GGG TTC TTG GGA GAT AA 1461
Leu Gly Phe Leu Gly Asp
            485 486
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CLONE C8.6

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G   GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
    Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
      1               5                  10
TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His
          15                  20                  25
AAT GTT TGG GCT ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                30                  35
AAC CCA CAA GAA GTA GTA TTG GAA AAT GTA ACA GAA AAT 154
Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn
 40                  45                  50
TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
            55                  60
GAG GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA AAG CCA 232
Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
 65                  70                  75
TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
          80                  85                  90
ACT AAT TTG GAG AAT GCT AAT AAT ACC GAG AAT GCT AAT 310
Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn
                95                  100
AAT ACC AAT AAT TAT ACC TTG GGG ATG GAG AGA GGT GAA 349
Asn Thr Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu
    105                 110                 115
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AGA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC TTA AGA 388
Arg Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Leu Arg
        120                 125
GAT AAG GGG AAA AAA GAA TAT GCA TTG TTT TAT AAA CTT 427
Asp Lys Gly Lys Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
130                 135                 140
GAT GTA GTA CAA ATA GAT AAT AGT ACC AAC TAT AGG CTG 466
Asp Val Val Gln Ile Asp Asn Ser Thr Asn Tyr Arg Leu
        145                 150                 155
ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
                160                 165
AAG GTA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT GCC 544
Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
    170                 175                 180
CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG AAG 583
Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys
                185                 190
TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGG ACA GTA 622
Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Arg Thr Val
195                 200                 205
CAA TGT ACA CAT GGA ATT AGA CCA GTA GTA TCA ACT CAA 661
Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
        210                 215                 220
CTA CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG ATA GTA 700
Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Ile Val
                225                 230
ATT AGA TCT GAA AAT ATC ACA GAC AAT GCT AAA ACC ATA 739
Ile Arg Ser Glu Asn Ile Thr Asp Asn Ala Lys Thr Ile
    235                 240                 245
ATA GTG CAG CTA AAT GAA TCT ATA GTG ATT AAT TGT ACA 778
Ile Val Gln Leu Asn Glu Ser Ile Val Ile Asn Cys Thr
            250                 255
AGA CCC AAT AAC AAC ACA AGA AAA AGT ATA AAT ATA GGA 817
Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn Ile Gly
260                 265                 270
CCA GGG AGA GCA TTC TAT ACA ACA GGA GAC ATA ATA GGA 856
Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
        275                 280                 285
GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AAA ACA CAA 895
Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln
                290                 295
TGG GAA AAA ACG TTA AGA CAG ATA GCT ATA AAA TTA GAA 934
Trp Glu Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu
    300                 305                 310
GAA AAA TTT AAG AAT AAA ACA ATA GCC TTT AAT AAA TCC 973
Glu Lys Phe Lys Asn Lys Thr Ile Ala Phe Asn Lys Ser
            315                 320
TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT 1012
Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn
325                 330                 335
TGT GGA GGG GGA TTT TTC TAC TGT AGT ACG AGA AAA CTG 1051
Cys Gly Gly Gly Phe Phe Tyr Cys Ser Thr Arg Lys Leu
        340                 345                 350
TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn
                355                 360
ACC GGG GAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
Thr Gly Asp Arg Thr Glu Glu Leu Asn Ile Thr Leu Pro
    365                 370                 375
TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val
            380                 385
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GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile
390                 395                 400
AGA TGT TCA TCA AAT ATT ACA GGG CTA CTA TTA AGG AGA 1246
Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Arg Arg
    405                 410                 415
GAT GGT GGA AGT AAC ACC AGT GAC AAC CAG ACT GAG ACC 1285
Asp Gly Gly Ser Asn Thr Ser Asp Asn Gln Thr Glu Thr
            420                 425
TTT AGA CCT GGG GGA GGA GAT ATG AGG GAC AAG TGG AGA 1324
Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Lys Trp Arg
430                 435                 440
AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro
        445                 450
TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTG GTG 1402
Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val
455                 460                 465
CAA AGA GAA AAA AGA GCA GTG GGG ATA GGA GCT ATG TTC 1441
Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
        470                 475                 480
CTT AGG TTC TTA GGA GAT AAA GCT TCT AGA GTC 1474
Leu Arg Phe Leu Gly Asp Lys Ala Ser Arg Val
            485                 490 491
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CLONE C15.2

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CTC GAG GTA CCT GTA TGG AAA GAA GCA ACT ACC ACT 36
Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
  1                 5                  10
CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
      15                  20                  25
AAA CAT AAT GTT TGG GCC ACA CAC GCC TGT GTA CCC ACA 114
Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
          30                  35
GAT CCC AAC CCA CAA GAA GTA GTA TTG GGA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Val Leu Gly Asn Val Thr
  40                  45                  50
GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
      55                  60
ATG CAT GAA GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA 231
Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
  65                  70                  75
AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA 270
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
      80                  85                  90
AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn
          95                  100
AGT AGT GCC ACT ACC AAT AGT AGT AGT TGG GAA GAA ATG 348
Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met
  105                 110                 115
AAG GGG GAA ATG AAA AGA TGC TCT TTC AAT ATC ACC ACA 387
Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr
      120                 125
AGC ATA AGA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe
130                 135                 140
TAT AGA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACC 465
Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr
      145                 150                 155
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ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr
                160                 165
CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile
    170                 175                 180
CAT TTT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys
            185                 190
AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn
195                 200                 205
GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660
Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val
        210                 215                 220
GTG TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA 699
Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
            225                 230
GAA GAG GTA ATA ATT AGA TCT GAC AAT ATC ACA GAC AAT 738
Glu Glu Val Ile Ile Arg Ser Asp Asn Ile Thr Asp Asn
    235                 240                 245
ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
Thr Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Val
            250                 255
ATT AAT TGT ACA AGA CCC AAC AAC AAT ACA AGA AAA AGT 816
Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Ser
260                 265                 270
ATA CAT ATA GGA CCA GGG AGT GCA TTT TTT GCA ACA GGA 855
Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
        275                 280                 285
GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894
Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu
            290                 295
AGT AGA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val
    300                 305                 310
ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu
            315                 320
AAA ACA ATA GTC TTT AAT CGA TCC TCA GGA GGG GAC CCG 1011
Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro
325                 330                 335
GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe
        340                 345                 350
TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
            355                 360
AAT GTT ACT AAA GGG TTG AAT AAC ACT GAA GGA AAT AGC 1128
Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
    365                 370                 375
ACA GGA GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys
            380                 385
CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
390                 395                 400
TAT GCC CCT CCC ATC AGT GGA CAA ATT AGA TGT TCA TCA 1245
Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser
        405                 410                 415
AAC ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT AGT 1284
Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser
            420                 425
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AAG AAC GAG AGC ATC ACC ACC GAG GTC TTC AGA CCT GGA 1323
Lys Asn Glu Ser Ile Thr Thr Glu Val Phe Arg Pro Gly
    430                 435                 440
GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT GAA TTA TAT 1362
Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
            445                 450
AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCG 1401
Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
455                 460                 465
CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA 1440
Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
        470                 475                 480
AGA GCA GTG GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
                485                 490
TTG GGA GCA TAA AGC TTC TAG AGT CGA CCT GCA 1512
Leu Gly Ala Xaa Ser Phe Xaa Ser Arg Pro Ala
    495                 500                 504

                                CLONE C15.3
    CTC GAG GTA CCT GTG TGG AAA GAA GCA ACT ACC ACT 36
    Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
      1                 5                  10
CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
          15                  20                  25
AAA CAT AAT GTT TGG GCC ACA CAC GCC TGT GTA CCC ACA 114
Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
                30                  35
GAT CCC AAC CCA CAA GAA GTA GTA TTG GGA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Val Leu Gly Asn Val Thr
    40                  45                  50
GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
            55                  60
ATG CAT GAA GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA 231
 Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65                  70                  75
AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA 270
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
        80                  85                  90
AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn
                95                  100
AGC AGT GCC ACT ACC AAT AGT AGT AGT TGG GAA GAA ATG 348
Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met
    105                 110                 115
AAG GGG GAA ATG AAA AGG TGC TCT TTC AAT ATC ACC ACA 387
Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr
            120                 125
AGC ATA AGA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe
130                 135                 140
TAT AGA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACC 465
Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr
        145                 150                 155
ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr
                160                 165
CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile
    170                 175                 180
CAT TTT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
His Ph  Cys Ala Pro Ala Gly Phe Ala Ile L u Lys Cys
            185                 190
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AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn
195                 200                 205
GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660
Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val
        210                 215                 220
GTG TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA 699
Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
                225                 230
GAA GAG GTA ATA ATT AGA TCT GGC AAT ATC ACA GAC AAT 738
Glu Glu Val Ile Ile Arg Ser Gly Asn Ile Thr Asp Asn
    235                 240                 245
ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
Thr Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Val
            250                 255
ATT AAT TGT ACA AGA TCC AAC AAC AAT ACA AGA AAA AGT 816
Ile Asn Cys Thr Arg Ser Asn Asn Asn Thr Arg Lys Ser
260                 265                 270
ATA CAT ATA GGA CCA GGG AGT GCA TTT TTT GCA ACA GGA 855
Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
        275                 280                 285
GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894
Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu
                290                 295
AGT AGA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val
    300                 305                 310
ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu
            315                 320
AAA ACA ATA GTC TTT AAT CGA TCC TCA GGA GGG GAC CCG 1011
Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro
325                 330                 335
GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe
        340                 345                 350
TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
                355                 360
AAT GTT ACT AAA GGG TTG AAT AAC ACT GAA GGA AAT AGC 1128
Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
    365                 370                 375
ACA GGG GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys
            380                 385
CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
390                 395                 400
TAT GCC CCT CCC ATC AGT GGA CAA ATT AGA TGT TCA TCA 1245
Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser
        405                 410                 415
AAT ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT AGT 1284
Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser
                420                 425
AAG AAC GAG AGC ATC ACC ACC GAG GTC TTC AGA CCT GGA 1323
Lys Asn Glu Ser Ile Thr Thr Glu Val Phe Arg Pro Gly
    430                 435                 440
GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT GAA TTA TAT 1362
Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
            445                 450
AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCG 1401
Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
455                 460                 465
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CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA 1440
Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
    470                 475                 480
AGA GCA GTG GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
            485                 490
TTA GGA GCA TAA AGC TTC TAG A 1501
Leu Gly Ala Xaa Ser Phe Xaa
495                 500
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CLONE C7.2

```
GG  GAA TTC GGA TCC GGG GTA CCT GTG TGG AAG GAA GCA 38
    Glu Phe Gly Ser Gly Val Pro Val Trp Lys Glu Ala
      1               5                  10
ACC ACC ACT CTA TTC TGT GCA TCA GAT GCT AGA GCA TAT 77
Thr Thr Thr Leu Phe Cys Ala Ser Asp Ala Arg Ala Tyr
        15                  20                  25
GAC ACA GAG GTA CAT AAT GTT TGG GCC ACA CAT GCC TGT 116
Asp Thr Glu Val His Asn Val Trp Ala Thr His Ala Cys
                30                  35
GTA CCC ACA GAC CCT AGT CCA CAA GAA GTA GTT TTG GAA 155
Val Pro Thr Asp Pro Ser Pro Gln Glu Val Val Leu Glu
    40                  45                  50
AAT GTG ACA GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG 194
Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met
            55                  60
GTA GAA CAA ATG CAT GAG GAT ATA ATT AGT TTA TGG GAT 233
Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp
 65                  70                  75
CAA AGC TTA AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT 272
Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys
        80                  85                  90
GTT ACT TTA AAT TGC AGT GAT TAT AGG AAT GCT ACT GAT 311
Val Thr Leu Asn Cys Ser Asp Tyr Arg Asn Ala Thr Asp
                95                  100
TAT AAG AAT GCT ACT GAT ACC ACT AGT AGT AAC GAG GGA 350
Tyr Lys Asn Ala Thr Asp Thr Thr Ser Ser Asn Glu Gly
    105                 110                 115
AAG ATG GAG AGA GGA GAA ATA AAA AAC TGC TCT TTC AAT 389
Lys Met Glu Arg Gly Glu Ile Lys Asn Cys Ser Phe Asn
            120                 125
ATT ACC ACA AGC ATA AAA AAT AAG ATG CAG AAA GAA TAT 428
Ile Thr Thr Ser Ile Lys Asn Lys Met Gln Lys Glu Tyr
130                 135                 140
GCA CTT TTC TAT AAA CTT GAT ATA GTA CCA ATA GAT AAT 467
Ala Leu Phe Tyr Lys Leu Asp Ile Val Pro Ile Asp Asn
        145                 150                 155
ACA AGC TAT ACA TTG ATA AGT TGT AAC ACC TCA GTC ATT 506
Thr Ser Tyr Thr Leu Ile Ser Cys Asn Thr Ser Val Ile
                160                 165
ACA CAG GCC TGT CCA AAG GTA TCC TTT GAA CCA ACT CCC 545
Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Thr Pro
    170                 175                 180
ATA CAT TAT TGT GCT CCG GCT GGT TTT GCG ATT CTA AAG 584
Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys
            185                 190
TGT AAT GAT AAG AAG TTC AGT GGA AAA GGA GAA TGT AAA 623
Cys Asn Asp Lys Lys Phe Ser Gly Lys Gly Glu Cys Lys
195                 200                 205
AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AGG CCA 662
Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro
        210                 215                 220
GTA GTA TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA 701
Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
225                 230
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GAA GAA GAG GTG GTA ATT AGA TCT GAC AAT TTC ATA GAC 740
Glu Glu Glu Val Val Ile Arg Ser Asp Asn Phe Ile Asp
    235                 240                 245
AAT ACT AAA ACC ATA ATA GTA CAG CTG AAA GAA TCT GTA 779
Asn Thr Lys Thr Ile Ile Val Gln Leu Lys Glu Ser Val
            250                 255
GAA ATT AAT TGT ATA AGA CCC AAC AAT AAT ACA AGA AAA 818
Glu Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr Arg Lys
260                 265                 270
GGT ATA CAT ATA GGA CCA GGG AGA GCA TGG TAT GCA ACA 857
Gly Ile His Ile Gly Pro Gly Arg Ala Trp Tyr Ala Thr
        275                 280                 285
GGA GAA ATA GTA GGA GAT ATA AGA AAG GCA TAT TGT AAC 896
Gly Glu Ile Val Gly Asp Ile Arg Lys Ala Tyr Cys Asn
            290                 295
ATT AGT AGA ACA AAA TGG AAT AAC ACT TTA ATA CAG ATA 935
Ile Ser Arg Thr Lys Trp Asn Asn Thr Leu Ile Gln Ile
    300                 305                 310
GCT AAC AAA TTA AAA GAA AAA TAT AAT ACA ACA ATA AGC 974
Ala Asn Lys Leu Lys Glu Lys Tyr Asn Thr Thr Ile Ser
            315                 320
TTT AAT CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ACG 1013
Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Thr
325                 330                 335
CAT AGT TTT AAT TGT GGA GGG GAG TTT TTC TAC TGT GAT 1052
His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asp
        340                 345                 350
TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT TTA AAT GGT 1091
Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Leu Asn Gly
            355                 360
ACT TGG AAT TTT ACT GCA GGG TCA AAT GAA ACT GAA GGC 1130
Thr Trp Asn Phe Thr Ala Gly Ser Asn Glu Thr Glu Gly
    365                 370                 375
AAT ATC ACA CTC CCA TGC AGA ATA AAA CAA ATT ATA AAC 1169
Asn Ile Thr Leu Pro Cys Arg Ile Lys Gln Ile Ile Asn
            380                 385
AGG TGG CAG GAA GTA GGG AAA GCA ATG TAT GCC CCT CCC 1208
Arg Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro Pro
390                 395                 400
ATC AGT GGA CAA ATA AAA TGC TCA TCA AAC ATT ACA GGG 1247
Ile Ser Gly Gln Ile Lys Cys Ser Ser Asn Ile Thr Gly
        405                 410                 415
ATG ATA TTA ACA AGG GAT GGT GGT AAC GAG AAC AAT AAT 1286
Met Ile Leu Thr Arg Asp Gly Gly Asn Glu Asn Asn Asn
            420                 425
GAG AGC AGT ACT ACT GAG ACC TTC AGA CCG GGA GGA GGA 1325
Glu Ser Ser Thr Thr Glu Thr Phe Arg Pro Gly Gly Gly
    430                 435                 440
GAT ATG AGG AAC AAT TGG AGA AGT GAA TTA TAT AAA TAT 1364
Asp Met Arg Asn Asn Trp Arg Ser Glu Leu Tyr Lys Tyr
            445                 450
AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCA CCC ACC 1403
Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr
455                 460                 465
AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA AGA GCA 1442
Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala
        470                 475                 480
GTG GGA GCG CTA GGA GCT ATG TTC CTT GGG TTC TTA GGA 1481
Val Gly Ala Leu Gly Ala Met Phe Leu Gly Phe Leu Gly
            485                 490
GCA TAA AGC TTC TAG ACC GAC TCT AGA GGA TCC 1514
Ala Xaa Ser Phe Xaa Thr Asp Ser Arg Gly Ser
    495                 500             504
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CLONE C7.10

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      G   GTA CCT GTG TGG AAG GAA GCA ACC ACC ACT CTA TTC 37
          Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
            1               5                  10
 5    TGT GCA TCA GAT GCT AGA GCA TAT GAC ACA GAG GTA CAT 76
      Cys Ala Ser Asp Ala Arg Ala Tyr Asp Thr Glu Val His
              15                  20                  25
      AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC CCT 115
      Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
10                30                  35
      AGT CCA CAA GAA GTA TTT TTG GGA AAT GTG ACA GAA AAT 154
      Ser Pro Gln Glu Val Phe Leu Gly Asn Val Thr Glu Asn
          40                  45                  50
      TTT AAT ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG TAT 193
15    Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met Tyr
                55                  60
      GAG GAT ATA ATT AGT TTA TGG GAT CAA AGC TTA AAG CCA 232
      Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
       65                  70                  75
20    TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
      Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
              80                  85                  90
      AGT GAT TAT AGG AAT GCT ACT GAT TAT AAG AAT GCT ACT 310
      Ser Asp Tyr Arg Asn Ala Thr Asp Tyr Lys Asn Ala Thr
25                95                 100
      GAT ACC ACT AGT AGT AAC GAG GGA AAG ATG GAG AGA GGA 349
      Asp Thr Thr Ser Ser Asn Glu Gly Lys Met Glu Arg Gly
          105                 110                 115
      GAA ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC ATA 388
30    Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile
                120                 125
      AAA AAT AAG ATG CAG AAA GAA TAT GCA CTT TTC TAT AAA 427
      Lys Asn Lys Met Gln Lys Glu Tyr Ala Leu Phe Tyr Lys
      130                 135                 140
35    CTT AAT ATA GTA CCA ATA GAT AAT ACA AGC TAT ACA TTG 466
      Leu Asn Ile Val Pro Ile Asp Asn Thr Ser Tyr Thr Leu
              145                 150                 155
      ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
      Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
40                160                 165
      AAG GTA TCC TTT GAA CCA ATT CCC ATA CAT TAT TGT GCT 544
      Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
          170                 175                 180
      CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG AAG 583
45    Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys
                185                 190
      TTC AGT GGA AAA GGA GAA TGT AAA AAT GTC AGC ACA GTA 622
      Phe Ser Gly Lys Gly Glu Cys Lys Asn Val Ser Thr Val
      195                 200                 205
50    CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT CAA 661
      Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
              210                 215                 220
      CTG CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTG GTA 700
      Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Val
55                225                 230
      ATT AGA TCT GAC AAT TTC ACA GAC AAT ACT AAA ACC ATA 739
      Ile Arg Ser Asp Asn Phe Thr Asp Asn Thr Lys Thr Ile
          235                 240                 245
      ATA GTA CAG CTG AAA GAA TCT GTA GAA ATT AAT TGT ATA 778
60    Ile Val Gln Leu Lys Glu Ser Val Glu Ile Asn Cys Ile
                250                 255
      AGA CCC AAC AAT AAT ACA AGA AAA GGT ATA CAT ATA GGA 817
      Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Ile Gly
      260                 265                 270
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CCA GGG AGA GCA TGG TAT GCA ACA GGA GAA ATA GTA GGA 856
Pro Gly Arg Ala Trp Tyr Ala Thr Gly Glu Ile Val Gly
        275                 280                 285
GAT ATA AGA CAG GCA TAT TGT AAC ATT AGT AGA ACA AAA 895
Asp Ile Arg Gln Ala Tyr Cys Asn Ile Ser Arg Thr Lys
                290                 295
TGG AAT AAC ACT TTA ATA CAG ATA GCT AAC AAA TTA AAA 934
Trp Asn Asn Thr Leu Ile Gln Ile Ala Asn Lys Leu Lys
    300                 305                 310
GAA AAA TAT AAT ACA ACA ATA AGC TTT AAT CGA TCC TCA 973
Glu Lys Tyr Asn Thr Thr Ile Ser Phe Asn Arg Ser Ser
            315                 320
GGA GGG GAC CCA GAA ATT GTA ACC CAT AGT TTT AAT TGT 1012
Gly Gly Asp Pro Glu Ile Val Thr His Ser Phe Asn Cys
325                 330                 335
GGA GGG GAA TTT TTC TAC TGT AAT TCA ACA CAA CTG TTT 1051
Gly Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Leu Phe
        340                 345                 350
AAT AGT ACT TGG AAT TTA AAT GGT ACT TGG AAT TTT ACT 1090
Asn Ser Thr Trp Asn Leu Asn Gly Thr Trp Asn Phe Thr
            355                 360
GCA GGG TCA AAT GAA ACT GAA GGC AAT ATC ACA CTC CCA 1129
Ala Gly Ser Asn Glu Thr Glu Gly Asn Ile Thr Leu Pro
    365                 370                 375
TGC AGA ATA AAA CAA ATT ATA AAC AGG TGG CAG GAA GTA 1168
Cys Arg Ile Lys Gln Ile Ile Asn Arg Trp Gln Glu Val
            380                 385
GGA AAA GCA ATG TAT GCC CCT CCC ATC AGT GGA CAA ATA 1207
Gly Lys Ala Met Tyr Ala Pro Pro Ile Ser Gly Gln Ile
390                 395                 400
AGA TGC TCA TCA AAC ATT ACA GGG ATG ATA TTA ACA AGG 1246
Arg Cys Ser Ser Asn Ile Thr Gly Met Ile Leu Thr Arg
        405                 410                 415
GAT GGT GGT AAC GAG AAC AAT AAT GAG AGC AGT ACT ACT 1285
Asp Gly Gly Asn Glu Asn Asn Asn Glu Ser Ser Thr Thr
            420                 425
GAG ACC TTC AGA CCG GGA GGA GGA GAT ATG AGG AAC AAT 1324
Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asn Asn
    430                 435                 440
TGG AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT 1363
Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile
            445                 450
GAG CCA TTA GGA GTA GCA CCC ACC GAC TCT AGA GGA TCC 1402
Glu Pro Leu Gly Val Ala Pro Thr Asp Ser Arg Gly Ser
455                 460                 465
TCT AGA 1408
Ser Arg
    469
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CLONE C11.5

```
GAG GTA CCT GTG TGG AAA GAA GCA ACC ACT ACT CTA 36
Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
  1               5                  10
TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GGG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Gly Val
          15                  20                  25
CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
              30                  35
CCC AAC CCA CAA GAA ATA GAA TTG GTA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Ile Glu Leu Val Asn Val Thr Glu
      40                  45                  50
GAT TTT AAC ATG TGG AAA AAT AAA ATG GTA GAC CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Lys Met Val Asp Gln Met
          55                  60
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CAT GAG GAT ATA ATC AGT TTA TGG GAT GAA AGC CTA AAG 231
His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser Leu Lys
 65                  70                  75
CCA TGT GTA AAG TTA ACC CCA CTT TGT GTT ACT CTA AAC 270
Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
            80                  85                  90
TGC AGT GAT GTG AAC AAT TCC ACA AAT CCT AAT GAT ACT 309
Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr
                95                 100
AAT ACT AAT TCC ACT AAT ACT ACT TCC TCT ACT CCT ACG 348
Asn Thr Asn Ser Thr Asn Thr Thr Ser Ser Thr Pro Thr
    105                 110                 115
GCC ACT ACT AGT AGC GAG GAA AAG ATG GAG AAG GGA GAA 387
Ala Thr Thr Ser Ser Glu Glu Lys Met Glu Lys Gly Glu
            120                 125
ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA CAC ATG AAA 426
Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr His Met Lys
130                 135                 140
GAT AAG GCA CAG AAA GAA TAT GCA CTT TTT TAT AAA CTT 465
Asp Lys Ala Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
        145                 150                 155
GAT ATA GTA CCA ATA GAT GAT AAT AAT GCC AGC TAT AGG 504
Asp Ile Val Pro Ile Asp Asp Asn Asn Ala Ser Tyr Arg
                160                 165
TTG ATA AGT TGT AAT ACC TCA GAC ATT ACA CAG GCC TGT 543
Leu Ile Ser Cys Asn Thr Ser Asp Ile Thr Gln Ala Cys
    170                 175                 180
CCA AAG GTG ACC TTT GAG CCA ATT CCC ATA CAT TAT TGT 582
Pro Lys Val Thr Phe Glu Pro Ile Pro Ile His Tyr Cys
            185                 190
GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG 621
Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys
195                 200                 205
AAG TTC AAT GGA ACA GGA CCA TGT TCA AAG GTC AGC ACA 660
Lys Phe Asn Gly Thr Gly Pro Cys Ser Lys Val Ser Thr
        210                 215                 220
GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 699
Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
                225                 230
CAA CTG TTG TTA AAT GGC AGT CTT GCA GAA GAA GAA GTA 738
Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
    235                 240                 245
GTA ATT AGA TCT GTC AAT TTC ACA GAC AAT GCT AAA ATC 777
Val Ile Arg Ser Val Asn Phe Thr Asp Asn Ala Lys Ile
            250                 255
ATA ATA GTA CAG CTG AAA GAA CCT GTA GCA ATT AAT TGT 816
Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile Asn Cys
260                 265                 270
ACA AGA CCC AAC AAC AAT ACA AGA AAA GGT ATA CAT CTA 855
Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Leu
        275                 280                 285
GGA CCA GGG AGC ACA TTT TAT ACA ACA GGA GAA ATA ATA 894
Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile
                290                 295
GGA GAC ATA AGA AAA GCA TAT TGC AAG ATT AGT AAA GAA 933
Gly Asp Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu
    300                 305                 310
AAA TGG AAT AAC ACT TTA AGA CAG GTA GTT AAA AAA TTA 972
Lys Trp Asn Asn Thr Leu Arg Gln Val Val Lys Lys Leu
            315                 320
AGA GAA CAA TTT GGG AAT AAA ACA ATA ATT TTT AAT CGA 1011
Arg Glu Gln Phe Gly Asn Lys Thr Ile Ile Phe Asn Arg
325                 330                 335
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TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT 1050
Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe
        340                 345                 350
AAC TGT GGA GGG GAG TTT TTC TAC TGT AAT ACA ACA CAA 1089
Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Gln
                355                 360
CTG TTT AAT AGT ACT TGG AAT AAT ACT GAA GGG ACA AAT 1128
Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr Asn
    365                 370                 375
AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167
Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg
            380                 385
ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA AAA 1206
Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
390                 395                 400
GCA ACG TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
        405                 410                 415
ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
Ile Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly
                420                 425
GGT AGG AAT GTC ACA AAC AAT ACC GAA ACC TTC AGA CCT 1323
Gly Arg Asn Val Thr Asn Asn Thr Glu Thr Phe Arg Pro
    430                 435                 440
GGA GGA GGA GAC ATG AGG GAC AAT TGG AGA AGT GAA TTA 1362
Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
            445                 450
TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
455                 460                 465
GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAC AGA GAC 1440
Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
        470                 475                 480
AAA AGA GCA GCA CTA GGA GCC TTG TTC CTT GGG TTC TTA 1479
Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
                485                 490
GGA GCA TAA AAG CTT CTA GA 1499
Gly Ala Xaa Lys Leu Leu
    495             499
```

CLONE C11.7

```
GAG GTA CCT GTA TGG AAA GAA GCA ACC ACT ACT CTA 36
Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
  1               5                  10
TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
      15                  20                  25
CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
              30                  35
CCC AAC CCA CAA GAA ATA GAA TTG GTA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Ile Glu Leu Val Asn Val Thr Glu
          40                  45                  50
GAT TTT AAC ATG TGG AAA AAT AAA ATG GTA GAC CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Lys Met Val Asp Gln Met
                  55                  60
CAT GAG GAT ATA ATC AGT TTA TGG GAT GAA AGC CTA AAG 231
His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser Leu Lys
  65                  70                  75
CCA TGT GTA AAG TTA ACC CCA CTT TGT GTT ACT CTA AAC 270
Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
      80                  85                  90
TGC AGT GAT GTG AAC AAT TCC ACA AAT CCT AAT GAT ACT 309
Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr
              95                  100
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AAT ACT AAT TCC ACT AAT ACT ACT TCC TCT ACT CCT ACG 348
Asn Thr Asn Ser Thr Asn Thr Thr Ser Ser Thr Pro Thr
    105                 110                 115
GCC ACT ACT AGT AGC GAG GAA AAG ATG GAG AAG GGA GAA 387
Ala Thr Thr Ser Ser Glu Glu Lys Met Glu Lys Gly Glu
            120                 125
ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA CAC ATG AAA 426
Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr His Met Lys
130                 135                 140
GAT AAG GTA CAG AAA GAA TAT GCA CTT TTT TAT AAA CTT 465
Asp Lys Val Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
        145                 150                 155
GAT ATA GTA CCA ATA GAT GAT AAT AAT ACC AGC TAT AGG 504
Asp Ile Val Pro Ile Asp Asp Asn Asn Thr Ser Tyr Arg
                160                 165
TTG ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT 543
Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
    170                 175                 180
CCA ATG GTG ACC TTT GAG CCA ATT CCC ATA CAT TAT TGT 582
Pro Met Val Thr Phe Glu Pro Ile Pro Ile His Tyr Cys
            185                 190
GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG 621
Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys
195                 200                 205
AAG TTC AAT GGA ACA GGA CCA TGT TCA AAG GTC AGC ACA 660
Lys Phe Asn Gly Thr Gly Pro Cys Ser Lys Val Ser Thr
        210                 215                 220
GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 699
Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
                225                 230
CAA CTG TTG TTA AAT GGC AGT CTT GCA GAA GAA GAA GTA 738
Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
    235                 240                 245
GTA ATT AGA TCT GTC AAT TTC ACA GAC AAT GCT AAA ATC 777
Val Ile Arg Ser Val Asn Phe Thr Asp Asn Ala Lys Ile
            250                 255
ATA ATA GTA CAG CTG AAA GAA CCT GTA GCA ATT AAT TGT 816
Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile Asn Cys
260                 265                 270
ACA AGA CCC AAC AAC AAT ACA AGA AAA GGT ATA CAT CTA 855
Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Leu
        275                 280                 285
GGA CCA GGG AGC ACA TTT TAT ACA ACA GGA GAA ATA ATA 894
Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile
                290                 295
GGA GAC ATA AGA AAA GCA TAT TGC AAG ATT AGT AAA GAA 933
Gly Asp Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu
    300                 305                 310
AAA TGG AAT AAC ACT TTA AGA CAG GTA GTT AAA AAA TTA 972
Lys Trp Asn Asn Thr Leu Arg Gln Val Val Lys Lys Leu
            315                 320
AGA GAA CAA TTT GGG AAT AAA ACA ATA ATT TTT AAT CGA 1011
Arg Glu Gln Phe Gly Asn Lys Thr Ile Ile Phe Asn Arg
325                 330                 335
TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT 1050
Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe
        340                 345                 350
AAC TGT GGA GGG GAG TTT TTC TAC TGT AAT ACA ACA CAA 1089
Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Gln
                355                 360
CTG TTT AAT AGT ACT TGG AAT AAT ACT GAA GGG ACA AAT 1128
Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr Asn
    365                 370                 375
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      AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167
      S r Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg
                  380                 385
      ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA AAA 1206
 5    Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
      390                 395                 400
      GCA ACG TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
      Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
            405                 410                 415
10    ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
      Ile Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly
                  420                 425
      GGT AGG AAT GTC ACA AAC AAT ACC GAN NCC TTC AGA CCT 1323
      Gly Arg Asn Val Thr Asn Asn Thr Xaa Xaa Phe Arg Pro
15         430                 435                 440
      GGA GGA GGA GAC ATG AGG GAC AAT TGG AGA AGT GAA TTA 1362
      Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
                  445                 450
      TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
20    Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
      455                 460                 465
      GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAC AGA GAC 1440
      Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
            470                 475                 480
25    AAA AGA GCA GCA CTA GGA GCT TTG TTC CTT GGG TTC TTA 1479
      Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
                  485                 490
      GGA GCA TAA AAG CTT CTA GA 1499
      Gly Ala Xaa Lys Leu Leu
30         495                 499
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CLONE C10.5

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      G   GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
          Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
35          1               5                  10
      TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
      Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
                15                  20                  25
      AAT GTT TGG GCA ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
40    Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                      30                  35
      AAC CCA CAA GAA ATA GTA TTG GGA AAT GTG ACA GAA AAT 154
      Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
           40                  45                  50
45    TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
      Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
                     55                  60
      GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
      Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro
50     65                  70                  75
      TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
      Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
                80                  85                  90
      AAG GAT CTG GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
55    Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
                           95                  100
      ACC AAT AAT AGT AGT TTG GAG GGA CTA AGA GAA CAA ATG 349
      Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
          105                 110                 115
60    ACA AAC TGC TCT TTC AAC ATC ACC ACA AGT ATA AGA GAT 388
      Thr Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
                      120                 125
      AAG GTG CAG AAA GAA TAT GCA CTT TTG TAT AAA CTT GAT 427
      Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
65    130                 135                 140
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GTA GTA CCA ATA GAA GAA GAT GAC AAT ACT AGC TAT AGA 466
Val Val Pro Il  Glu Glu Asp Asp Asn Thr Ser Tyr Arg
        145                 150                 155
TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCT TGT 505
Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
                160                 165
CCA AAG ACA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT 544
Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
    170                 175                 180
GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG 583
Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys
                185                 190
AAG TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGC ACA 622
Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr
195                 200                 205
GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 661
Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
        210                 215                 220
CAA CTG TTG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTA 700
Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
                225                 230
GTA ATC AGA TCT GCC AAT TTC ACA GAC AAT GCT AAA ACC 739
Val Ile Arg Ser Ala Asn Phe Thr Asp Asn Ala Lys Thr
    235                 240                 245
ATA ATA GTA CAT CTA AAT GAA ACT GTA AAA ATT AAT TGT 778
Ile Ile Val His Leu Asn Glu Thr Val Lys Ile Asn Cys
                250                 255
ACA AGA CTT GGC AAC AAT ACA AGA AAA AGT ATA AAT ATA 817
Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile Asn Ile
260                 265                 270
GGA CCA GGG AGA GTA CTC TAT GCA ACA GGA GAA ATA ATA 856
Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile
        275                 280                 285
GGA GAC ATA AGA CAA GCA CAT TGT AAC ATT AGT AGA GCA 895
Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala
                290                 295
CAA TGG AAT AAG ACT TTA GAA AAG GTA GTT GAC AAA TTA 934
Gln Trp Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu
    300                 305                 310
AGA AAA CAA TTT GGG GAT AAT ACA ACA ATA GCT TTT AAT 973
Arg Lys Gln Phe Gly Asp Asn Thr Thr Ile Ala Phe Asn
                315                 320
CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC ACT 1012
Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Thr
325                 330                 335
TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA 1051
Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr
        340                 345                 350
CAA CTG TTT AAT AGT ACT TGG AAT AAT ACT TGG AAG GAT 1090
Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Trp Lys Asp
                355                 360
CCT AAC AGG AGT GAC AAT ATC ACA CTC CCA TGC AGA ATA 1129
Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg Ile
    365                 370                 375
AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA 1168
Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala
                380                 385
ATG TAC GCC CCT CCC ATC AGA GGG GAA ATT AGA TGT TCA 1207
Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser
390                 395                 400
TCA AAT ATC ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT 1246
Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly
        405                 410                 415
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AAT GAC GAT GGT AAT GAC ACG ACC ACA AAC AGG ACC GAG 1285
Asn Asp Asp Gly Asn Asp Thr Thr Thr Asn Arg Thr Glu
                420                 425
ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1324
Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
    430                 435                 440
AGA AGT GAA TTA TAT AGA TAT AAA GTA GTA AAA ATT GAA 1363
Arg Ser Glu Leu Tyr Arg Tyr Lys Val Val Lys Ile Glu
            445                 450
CCA TTA GGA ATA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1402
Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg Arg Val
455                 460                 465
GTG CAG AGA GAA AAA AGA GCA GTA GGA CTA GGA GCT TTG 1441
Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
        470                 475                 480
TTC CTT GGG T TCTTAGGAG CATAAAGCTT CTAGA 1475
Phe Leu Gly
        483
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CLONE C10.7

```
G   GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
    Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
      1               5                  10
TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
          15                  20                  25
AAT GTT TGG GCA ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
              30                  35
AAC CCA CAA GAA ATA GTA TTG GGA AAT GTG ACA GAA AAT 154
Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
    40                  45                  50
TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
        55                  60
GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro
 65                  70                  75
TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
            80                  85                  90
AAG GAT CTG GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
                95                  100
ACC AAT AAT AGT AGT TTG GAG GGA CTA AGA GAA CAA ATG 349
Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
    105                 110                 115
ACA AAC TGC TCT TTC AAC ATC ACC ACA AGT ATA AGA GAT 388
Thr Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
            120                 125
AAG GTG CAG AAA GAA TAT GCA CTT TTG TAT AAA CTT GAT 427
Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
130                 135                 140
GTA GTA CCA ATA GAA GAA GAT GAC AAT ACT AGC TAT AGA 466
Val Val Pro Ile Glu Glu Asp Asp Asn Thr Ser Tyr Arg
        145                 150                 155
TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCT TGT 505
Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
                160                 165
CCA AAG ACA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT 544
Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
    170                 175                 180
GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG 583
Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys
        185                 190
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AAG TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGC ACA 622
Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr
195                 200                 205
GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 661
Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
        210                 215                 220
CAA CTG TTG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTA 700
Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
                225                 230
GTA ATC AGA TCT GCC AAT TTC ACA GAC AAT GCT AAA ACC 739
Val Ile Arg Ser Ala Asn Phe Thr Asp Asn Ala Lys Thr
    235                 240                 245
ATA ATA GTA CAT CTA AAT GAA ACT GTA AAA ATT AAT TGT 778
Ile Ile Val His Leu Asn Glu Thr Val Lys Ile Asn Cys
            250                 255
ACA AGA CTT GGC AAC AAT ACA AGA AAA AGT ATA AAT ATA 817
Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile Asn Ile
260                 265                 270
GGA CCA GGG AGA GTA CTC TAT GCA ACA GGA GAA ATA ATA 856
Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile
        275                 280                 285
GGA GAC ATA AGA CAA GCA CAT TGT AAC ATT AGT AGA GCA 895
Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala
                290                 295
CAA TGG AAT AAG ACT TTA GAA AAG GTA GTT GAC AAG TTA 934
Gln Trp Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu
    300                 305                 310
AGA AAA CAA TTT GGG GAT AAT ACA ACA ATA GCT TTT AAT 973
Arg Lys Gln Phe Gly Asp Asn Thr Thr Ile Ala Phe Asn
            315                 320
CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC ACT 1012
Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Thr
325                 330                 335
TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA 1051
Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr
        340                 345                 350
CAA CTG TTT AAT AGT ACT TGG AAT AAT ACT TGG AAG GAT 1090
Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Trp Lys Asp
                355                 360
CCT AAC AGG AGT GAC AAT ATC ACA CTC CCA TGC AGA ATA 1129
Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg Ile
    365                 370                 375
AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA 1168
Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala
            380                 385
ATG TAC GCC CCT CCC ATC AGA GGG GAA ATT AGA TGT TCA 1207
Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser
390                 395                 400
TCA AAT ATC ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT 1246
Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly
        405                 410                 415
AAT GAC GAT GGT AAT GAC ACG ACC ACA AAC AGG ACC GAG 1285
Asn Asp Asp Gly Asn Asp Thr Thr Thr Asn Arg Thr Glu
                420                 425
ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1324
Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
    430                 435                 440
AGA AGT GAA TTA TAT AGA TAT AAA GTA GTA AAA ATT GAA 1363
Arg Ser Glu Leu Tyr Arg Tyr Lys Val Val Lys Ile Glu
            445                 450
CCA TTA GGA ATA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1402
Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg Arg Val
455                 460                 465
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GTG CAG AGA GAA AAA AGA GCA GTA GGA CTA GGA GCT TTG 1441
Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
        470                 475                 480
TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1475
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
                485                 490 491
```

CLONE C17.1

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    CTC GAG GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT 36
    Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
      1               5                  10
CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT TCA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu
          15                  20                  25
GCA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA 114
Ala His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
                30                  35
GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr
     40                  45                  50
GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
               55                  60
ATG CAT GGG GAT ATA ATT AGT TTA TGG GAT CAA AGC CTA 231
Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65                  70                  75
AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACG TTA 270
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
          80                  85                  90
AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309
Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
                95                 100
ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 348
Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
     105                 110                 115
ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
               120                 125
CTT TTT TAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
130                 135                 140
AAT ACT AGC TAT AGG TTG ATA AGT TGT AAC ACC TCA GTC 465
Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
          145                 150                 155
ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
               160                 165
CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT CTA 543
Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
     170                 175                 180
AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
               185                 190
ACA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
195                 200                 205
CCA GTA GTA TCA ACT CAA CTG TTG TTA AAT GGC AGT CTA 660
Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
          210                 215                 220
GCA GAA GAA GAC ATA GTA ATT AGA TCC GCC AAT CTC ACA 699
Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
               225                 230
GAC AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 738
Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser
235                 240                 245
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GTA ACA ATG AAT TGT ACA AGA CCC AAC AAC AAT ACA ATG 777
Val Thr Met Asn Cys Thr Arg Pro Asn Asn Asn Thr Met
            250                 255
AAA AGT ATA CAT ATA GGA CCA GGC AGA GCA TTT TAT GCA 816
Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala
260                 265                 270
ACA GGA AAC ATA ATA GGA GAT ATA AGA CAA GCA CAT TGT 855
Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys
        275                 280                 285
AAC ATT AGT GGA ACA AAA TGG AAT GAC ACT TTG AAA AAG 894
Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys
                290                 295
ATA GCT ATA AAA TTA AGA GAA CAA TTT AAT AAG ACA ATA 933
Ile Ala Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile
    300                 305                 310
GTC TTT AAT CAA TCC TCA GGA GGG GAC CCA GAA ATT GCA 972
Val Phe Asn Gln Ser Ser Gly Gly Asp Pro Glu Ile Ala
            315                 320
ACG CTC AGT TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT 1011
Thr Leu Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys
325                 330                 335
AAT TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT AGT ACT 1050
Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Ser Thr
        340                 345                 350
GGG TCA AAT AAC ACT AAA GGA AAT GAC ACA ATC ACA CTC 1089
Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr Ile Thr Leu
                355                 360
CCA TGC AGA ATA AGA CAA ATT ATA AAC ATG TGG CAG AAA 1128
Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln Lys
    365                 370                 375
ATA GGA AAA GCA ATG TAT GCC CCT CCC ATC AAA GGG CAA 1167
Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln
            380                 385
ATT AGA TGT TCA TCA AAT ATT ACA GGG CTA ATA TTA ACA 1206
Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr
390                 395                 400
AGA GAT GGT GGT AAC AAC AAC ATG AGC AAG ACC ACC GAG 1245
Arg Asp Gly Gly Asn Asn Asn Met Ser Lys Thr Thr Glu
        405                 410                 415
ACC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1284
Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
                420                 425
AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT GAA 1323
Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
    430                 435                 440
CCA TTA GGA GTA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1362
Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val
            445                 450
GTG CAG AGA GAA AAA AGA GCA GTG GGA ATA GGA GCT GTG 1401
Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Val
455                 460                 465
TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1435
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
        470                 475         478
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CLONE C17.3

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CTC GAG GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT 36
Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
  1                 5                  10
CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT TCA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu
          15                  20                  25
GCA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA 114
Ala His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
                30                  35
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GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr
     40                  45                  50
GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
                 55                  60
ATG CAT GGG GAT ATA ATT AGT TTA TGG GAT CAA AGC CTA 231
Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65                  70                  75
AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACG TTA 270
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
           80                  85                  90
AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309
Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
                95                 100
ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 348
Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
    105                 110                 115
ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
           120                 125
CTT TTT TAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
130                 135                 140
AAT ACT AGC TAT AGG TTG ATA AGT TGT AAC ACC TCA GTC 465
Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
          145                 150                 155
ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
                160                 165
CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT CTA 543
Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
    170                 175                 180
AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
           185                 190
ACA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
195                 200                 205
CCA GTA GTA TCA ACT CAA CTG TTG TTA AAT GGC AGT CTA 660
Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
          210                 215                 220
GCA GAA GAA GAC ATA GTA ATT AGA TCC GCC AAT CTC ACA 699
Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
                225                 230
GAC AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 738
Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser
    235                 240                 245
GTA ACA ATG AAT TGT ACA AGA CCC AAC AAC AAT ACA ATG 777
Val Thr Met Asn Cys Thr Arg Pro Asn Asn Asn Thr Met
           250                 255
AAA AGT ATA CAT ATA GGA CCA GGC AGA GCA TTT TAT GCA 816
Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala
260                 265                 270
ACA GGA AAC ATA ATA GGA GAT ATA AGA CAA GCA CAT TGT 855
Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys
          275                 280                 285
AAC ATT AGT GGA ACA AAA TGG AAT GAC ACT TTG AAA AAG 894
Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys
                290                 295
ATA GCT ATA AAA TTA AGA GAA CAA TTT AAT AAG ACA ATA 933
Ile Ala Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile
    300                 305                 310
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GTC TTT AAT CAA TCC TCA GGA GGG GAC CCA GAA ATT GCA 972
Val Phe Asn Gln Ser Ser Gly Gly Asp Pro Glu Ile Ala
          315                 320
ACG CTC AGT TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT 1011
Thr Leu Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys
325                 330                 335
AAT TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT AGT ACT 1050
Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Ser Thr
          340                 345                 350
GGG TCA AAT AAC ACT AAA GGA AAT GAC ACA ATC ACA CTC 1089
Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr Ile Thr Leu
                    355                 360
CCA TGC AGA ATA AGA CAA ATT ATA AAC ATG TGG CAG AAA 1128
Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln Lys
    365                 370                 375
ATA GGA AAA GCA ATG TAT GCC CCT CCC ATC AAA GGG CAA 1167
Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln
          380                 385
ATT AGA TGT TCA TCA AAT ATT ACA GGG CTA ATA TTA ACA 1206
Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr
390                 395                 400
AGA GAT GGT GGT AAC AAC AAC ATG AGC AAG ACC ACC GAG 1245
Arg Asp Gly Gly Asn Asn Asn Met Ser Lys Thr Thr Glu
          405                 410                 415
ACC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1284
Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
                    420                 425
AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT GAA 1323
Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
    430                 435                 440
CCA TTA GGA GTA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1362
Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val
          445                 450
GTG CAG AGA GAA AAA AGA GCA GTG GGA ATA GGA GCT GTG 1401
Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Val
455                 460                 465
TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1435
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
          470                 475         478
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In addition to the listing in Table 1, Figure 3 shows the alignment of the amino acid sequences of the clones of each of the seven isolates. Corresponding residues from various clones are in boxes. In the figure, the amino acid sequences are aligned against MN-rgp120 (SEQ. ID. NO. 29).

In one embodiment, a gp120 polypeptide of this invention has the same amino acid sequence as the sequence of one of the breakthrough isolates. In another embodiment, the amino acid sequence is truncated, as described in detail hereinafter. In another embodiment, a gp120 polypeptide sequence of this invention contains a substitution, insertion, or

deletion (alteration) of one or more amino acids in the sequence of a breakthrough isolate. Usually, with the exception of amino acids that are not present in a truncated amino acid sequence and eliminate an epitope, a gp120 polypeptide of this invention will include alterations in the amino acid sequence of a breakthrough isolate that do not alter the polypeptide's ability to induce the same neutralizing antibodies as the amino acid sequence of the isolate.

In general, substitutions in the amino acid sequence of a gp120 polypeptide of this invention are conservative substitutions, particularly for amino acid residues in the V2, V3, and C4 domains of gp120, which domains contain neutralizing epitopes. However, non-conservative substitutions, particularly in domains that do not contain neutralizing epitopes are contemplated.

Conservative substitutions replace an amino acid with an amino acid of similar size and character. For example, a hydrophobic residue or hydrophilic residue is replaced with another hydrophobic residue or hydrophilic residue, respectively. Amino acids can be divided into the following groups: positively charged residues (K, R and H); negatively charged residues (D and E); amides (N and Q); aromatics (F, Y, and W); hydrophobics (P, G, A, V, L, I, and M); and uncharged residues (S and T). Usually, residues within a group are replaced with another member of the group.

In one embodiment, critical amino acid residues in the V2, V3, and C4 domains of gp120 are identical to the corresponding residues in a breakthrough isolate sequence. Critical amino acid residues in the V2, V3, and C4 domains of gp120 are described in the experimental section. In another embodiment, all amino

acid residues in the V2, V3, and C4 domains of gp120 are identical to corresponding residues in a breakthrough isolate sequence.

Oligonucleotide Encoding gp120 from Breakthrough Isolates

The present invention also provides novel oligonucleotides encoding gp120 from the breakthrough isolates which can be used to express gp120. An oligonucleotide of this invention encodes a polypeptide of this invention. The oligonucleotide can be DNA or RNA, usually DNA. Although numerous nucleotide sequences can encode the same amino acid sequence due to the degeneracy of the genetic code, conveniently, the oligonucleotides of this invention include a nucleotide sequence of a breakthrough isolate as illustrated in Table 1 (Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28). Usually, an oligonucleotide of this invention is less than about 5 kilobases (kb), preferably less than about 3 kb.

To express the encoded amino acid sequence, the oligonucleotide can be inserted into a transcription unit. The transcription unit can be inserted into a plasmid for production of cell lines, inserted into a virus (e.g.; vaccinia) or can be used directly as a DNA vaccine. Suitable transcription units for production of vaccine proteins are well known. A preferred expression vector, designated psvI6B5, is illustrated in Sequence ID No. 32. The vector includes an HSV-1 gD1 signal sequence joined to a linker sequence. The gp120 nucleotide sequence to be expressed starts with the Kpn I site of the gene. Since all gp120 or gp160 sequences contain this site, any gp120 nucleotide sequence can be analogously inserted into the vector and expressed. The vector ends with a polyA tail from SV40.

In addition to being useful to express a polypeptide sequence of this invention, the oligonucleotides of this invention can also be used in diagnostics to detect HIV isolates. For example, the oligonucleotide or a portion thereof encoding a neutralizing epitope can be used in branched chain DNA diagnostics or as a probe in in situ hybridization studies.

Vaccine preparation

A gp120 polypeptide of this invention from a selected breakthrough isolate(s) in a suitable carrier is used to make a subunit vaccine. The polypeptide can be used alone, but is generally administered in a multivalent subunit vaccine that includes gp120 MN. In addition to one or more gp120 polypeptides of this invention, the vaccine generally includes the MN polypeptide (hereinafter, MN-rgp120). The vaccine usually includes about 3 to about 5 different gp120 polypeptides, but 30 or more different gp120 polypeptides can be used.

Preparation of gp120 polypeptides for use in a vaccine is well known and is described hereinafter. With the exception of the use of the selected HIV isolate, the gp120 subunit vaccine prepared in the method does not differ from gp120 subunit vaccines of the prior art.

As with prior art gp120 subunit vaccines, gp120 at the desired degree of purity and at a sufficient concentration to induce antibody formation is mixed with a physiologically acceptable carrier. A physiologically acceptable carrier is nontoxic to a recipient at the dosage and concentration employed in the vaccine. Generally, the vaccine is formulated for injection, usually intramuscular or subcutaneous injection. Suitable carriers for injection include

sterile water, but preferably are physiologic salt solutions, such as normal saline or buffered salt solutions such as phosphate-buffered saline or ringer's lactate. The vaccine generally contains an adjuvant. Useful adjuvants include QS21 (Quillaja saponaria, commercially available from Cambridge Biotech, Worcester, MA), which stimulates cytotoxic T-cells, and alum (aluminum hydroxide adjuvant). Formulations with different adjuvants which enhance cellular or local immunity can also be used. In particular, immunopotentiators such as cytokines can be included in the vaccine. Examples of suitable immunopotentiating cytokines include interleukins, such as interleukin-2 (IL-2) and interleukin-12 (IL-12), and tumor necrosis factor-alpha (TNF-α).

Additional excipients that can be present in the vaccine include low molecular weight polypeptides (less than about 10 residues), proteins, amino acids, carbohydrates including glucose or dextrans, chelating agents such as EDTA, and other excipients that stabilize the protein or inhibit growth of microorganisms.

The vaccine can also contain other HIV proteins. In particular, gp41 or the extracellular portion of gp41 or HIV-1 core proteins such as P24, P17, and P55 can be present in the vaccine. Although the amino acid sequence of gp41 is more conserved than that of gp120, gp41 contains neutralizing epitopes. Preferably, any gp41 present in the vaccine is from an HIV isolate present in the vaccine. gp160 from an isolate used in the vaccine can replace gp120 in the vaccine or be used together with gp120 from the isolate. Alternatively, gp160 from a different isolate than those in the vaccine can additionally be present in the vaccine.

Vaccines according to the invention can also contain one or more soluble gp120 polypeptide

sequences, or fragments thereof, in combination with an engineered virus specifically designed to express proteins that induce a cytotoxic T-cell response. Suitable engineered viruses are derived from, for example, Canary Pox virus, vaccinia viruses, attenuated human herpes viruses (such as, e.g., herpes simplex viruses), and Varicella Zoster. Exemplary engineered viruses are modified to express any HIV protein capable of inducing a cytotoxic T-cell response, such as those described above. Typically, immunization with the gp120/engineered virus vaccine is followed by administration of one or more doses of the gp120 polypeptide sequence(s) to boost the immune response. If desired, viruses can be engineered to express one or more gp120 polypeptide sequences of the invention, or fragments thereof, and used in vaccines with or without soluble gp120 polypeptide sequences.

Vaccine formulations generally include a total of about 300 to 600 μg of gp120, conveniently in about 1.0 ml of carrier. Preferred formulations include use of twice the weight of a gp120 polypeptide in twice as600 μg alum. However, formulations having smaller amounts (e.g.; 50 μg per dose) are also used, generally with alum or other adjuvants. The amount of gp120 for any isolate present in the vaccine will vary depending on the immunogenicity of the gp120. For example, gp120 from some strains of HIV may be less immunogenic than gp120 from the MN strain (Sequence ID No. 29). If two strains having different immunogenicity are used in combination, empirical titration of the amount of each virus would be performed to determine the percent of the gp120 of each strain in the vaccine. For isolates having similar immunogenicity, approximately equal amounts of each isolate's gp120 would be present in the vaccine. For example, in a preferred embodiment, the vaccine includes gp120 from the MN and a strain of this

invention at concentrations of about 300 μg per strain in about 1.0 ml of carrier. When the vaccine includes gp120 from about 30 isolates, about 10 to about 50 μg can be used. Methods of determining the relative amount of an immunogenic protein in multivalent vaccines are well known and have been used, for example, to determine relative proportions of various isolates in multivalent polio vaccines.

The vaccines of this invention are administered in the same manner as prior art HIV gp120 subunit vaccines. In particular, the vaccines are generally administered at 0, 1, and at 6, 8 or 12 months, depending on the protocol. A preferred protocol includes administration at 0, 1, 6, and 12 months. Following the immunization procedure, annual or bi-annual boosts can be administered. However, during the immunization process and thereafter, neutralizing antibody levels can be assayed and the protocol adjusted accordingly.

The vaccine is administered to uninfected individuals. In addition, the vaccine can be administered to seropositive individuals to augment immune response to the virus, as with prior art HIV vaccines. It is also contemplated that DNA encoding the strains of gp120 for the vaccine can be administered in a suitable vehicle for expression in the host. In this way, gp120 can be produced in the infected host, eliminating the need for repeated immunizations. Preparation of gp120 expression vehicles is described hereinafter.

Although the gp120 isolates described herein can be used as a vaccine as described above, the amino acid sequences can also be used alone or in combinations in the same type of formulation for use as an immunogen, to induce antibodies that recognize the isolate(s) present in the immunogen. Immunogens are formulated in

the same manner as vaccines and can include the same excipients, etc. Antibodies induced by the immunogens can be used in a diagnostic to detect the HIV strain in the immunogen or to affinity purify the strain.

gp120 Polypeptide Sequences and Chemokine Receptors

While CD4 is the primary cellular receptor for HIV-1, it is not sufficient for entry of HIV-1 into cells. Co-receptors required in conjunction with CD4 have been identified. These co-receptors are members of the chemokine receptor family of seven-transmembrane G-protein coupled receptors. The chemokine superfamily is subdivided into two groups based on the amino terminal cysteine spacing. The CXC chemokines are primarily involved in neutrophil-mediated inflammation, and the CC chemokines tend to be involved in chronic inflammation. At least five CC chemokine receptors, designated CC-CKR1-5 (also known in the art as CCR1-5), and at least four CXC chemokine receptors, designated CXC-CKR1-4 (also known as CXCR-1-4), have been identified.

CXC-CKR-4 (CXCR-4), which has also been called the alpha-chemokine receptor fusin, serves as an entry cofactor for T-cell-tropic HIV-1 strains. CC-CKR-5 (CC-R5), which has been called beta-chemokine receptor, together with its related family members, such as CC-CKR-2b and CC-CKR3, serve as entry cofactors for macrophage-tropic HIV-1 strains. T-cell-tropic strains can infect primary T-cells and T-cell lines, but not macrophages, whereas macrophage-tropic strains can infect macrophages and primary T-cells, but not T-cell lines. T-cell- and macrophage-tropic strains are discussed more fully in Deng et. al., Nature 381:661-666 (1996), which is hereby incorporated by reference in its entirety. Examples of T-cell-tropic strains include laboratory isolates, such as IIIB and MN.

Macrophage-tropic strains include primary isolates, including but not limited to A244, GNE6, GNE8, and breakthrough viruses from vaccinees immunized with gp120-based vaccines. Dual-tropic strains can use both types of co-receptors, entering cells via CXC-CKR-4 or via one or more CC-CKR family members, preferably CC-CKR-5, CC-CKR-2b, or CC-CKR-3. While the present invention is not intended to be bound or limited by any one theory, the entry of T-cell tropic and macrophage-tropic HIV-1 strains is believed to provide a unifying explanation of the differences in cell tropism between viral strains, the resistance to HIV-1 infection by many CD4-transfected nonprimate cells, and the HIV-1-infection resistance of a portion of the human population.

Accordingly, in one embodiment is a vaccine containing (1) a first gp120 polypeptide sequence, or fragment thereof, from a macrophage-tropic HIV-1 strain and/or a second gp120 polypeptide sequence, or fragment thereof, from a T-cell tropic strain, in combination with (2) a breakthrough isolate HIV gp120 polypeptide sequence, or fragment thereof, from a vaccinee vaccinated with the first and/or second HIV gp120 polypeptide sequence. Preferably, the vaccine includes at least two gp120 polypeptide sequences that bind to different chemokine receptors. In one embodiment, the vaccine includes first and second gp120 polypeptide sequences that bind to different chemokine receptors. In addition, the breakthrough isolate gp120 polypeptide sequence can bind to a different chemokine receptor than the chemokine receptor(s) bound by either or both of the first and second gp120 polypeptide sequence(s).

A preferred T-cell tropic strain is a laboratory isolate, most preferably MN. Preferred macrophage-tropic viruses for use in the invention are GNE6 and GNE8, which are representative of the breakthrough

viruses disclosed herein and differ from MN in that their gp120s induce the formation of antibodies that recognize the gp120 sequences (e.g., the V3 domain) involved in binding to CC chemokine receptors, such as CXC-CKR-5.

In one embodiment, HIV infection is prevented by administering one or more chemokine receptor-binding gp120 polypeptide sequences, or fragment(s) thereof containing appropriate chemokine receptor-binding domains, in a vaccine, such as those described above. Preferably, the vaccine also includes one or more CD4-binding gp120 polypeptide sequences or appropriate fragments thereof. Such vaccines induce anti-HIV antibodies that inhibit viral gp120-chemokine receptor or -CD4 binding. In addition, such gp120 polypeptides can directly inhibit HIV infection by binding to one or more co-receptors for HIV infection, such as CD4 or a chemokine receptor, thus providing a prophylactic or therapeutic effect in treating HIV infection. Preferably, gp120 polypeptide sequences useful in this regard contain the T-cell binding (TCB) domain.

Various uses of chemokine receptor-binding gp120 polypeptides are discussed below with regard to the CC chemokine receptor family. However, those skilled in the art recognize that this discussion applies equally to CXC chemokine receptors that act as cofactors in HIV infection.

The gp120 polypeptides can be used as a composition containing one or more gp120 polypeptides, as described for use as a vaccine or immunogen. The composition can be administered, prophylactically or therapeutically, to a patient at risk of infection or in need of such treatment using the dosages and routes and means of administration described herein. However, chronic administration may be preferred and dosages can be adjusted accordingly. It is noted that in vivo

administration can also induce antibodies that bind viral gp120, further inhibiting virus binding to CC-CKR.

The gp120 polypeptides can also be used in screening assays to identify antagonists of CC-CKR. For example, candidate antagonists can be screened for inhibition of binding of gp120 to a CC-CKR CC-CKR receptor that is isolated and attached to a surface (e.g., plastic dish) or recombinantly or naturally expressed on the surface of a cell. Antagonists can either bind gp120 or bind receptor. Preferred candidate antagonists include gp120 compounds, small gp120 peptides (5 to 20 amino acids in length, preferably 7 to 10 amino acids in length) or peptidomimetics of gp120 that bind receptor, monoclonal antibodies that bind gp120, and small organic molecules that bind either gp120 or receptor.

The antibodies induced by the gp120 polypeptides can also be used to induce anti-idiotype antibodies that bind CC chemokines. These anti-idiotype antibodies can be screened for binding to an anti-gp120 polypeptide antibody and inhibiting gp120 from binding CC-CKR receptor. Such anti-idiotype antibodies mimic gp120 by binding to CC-CKR receptor. Such antibodies, preferably human antibodies, can be obtained in a number of ways, such as human antibodies from combinatorial libraries (e.g., Burton et al. Adv. Immunolo. (1994) 57:191-280). It is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, homozygous deletion of the antibody heavy-chain joining region (JH) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line

immunoglobulin gene array in such germ-line mutant mice results in the production of human antibodies upon antigen challenge as described in Jakobovitis et al., *Proc. Natl. Acad. Sci. USA* **90**: 2551 (1993); Jakobovits et al., *Nature* **362**:255-258 (1993); Bruggermann et al., *Year in Immuno.* **7**: 33 (1993).

Alternatively, phage display technology as described by McCafferty et al., *Nature* **348**:552-553 (1990) can be used to produce human antibodies and antibody fragments in vitro from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are closed in-frame either into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Phage display can be performed in a variety of formats as reviewed by, for example, Johnson, et al., *Current Opinion in Structural Biology* **3**:564-571 (1993).

Several sources of V-gene segments can be used for phage display. Clackson et al., Nature, 352: 624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors (or embryonic cells) can be constructed. It has been demonstrated that antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., J. Mol. Biol., 222: 581-597 (1991), or Griffith et al., EMBO J., 12: 725-734 (1993).

In a natural immune response, antibody genes accumulate mutations at a high rate (somatic hypermutation). Some of the changes introduced confer higher affinity, and B cells displaying high-affinity surface immunoglobulin are preferentially replicated and differentiated during subsequent antigen challenge. This natural process can be mimicked by employing the technique known as "chain shuffling" (Marks et al., *Bio/Technol.* **10**:779-783 [1992]). In this method, the affinity of "primary" human antibodies obtained by phage display can be improved by sequentially replacing the heavy and light chain V region genes with repertoires of naturally occurring variants (repertoires) of V domain genes obtained from unimmunized donors. This technique allows the production of antibodies and antibody fragments with affinities in the nM range. A strategy for making very large phage antibody repertoires has been described by Waterhouse et al., Nucl. Acids Res., 21: 2265-2266 (1993).

Accordingly, antibodies that bind CC-CKR can be obtained by screening antibodies or fragments thereof expressed on the surface of bacteriophage in combinatorial libraries or in other systems as described above with a gp120 monoclonal antibody that inhibits gp120 binding to receptor.

In addition to screening antibodies with a gp-120 antibody, random or combinatorial peptide libraries can be screened with either a gp120 antibody or the gp120 compounds of the invention. Approaches are available for identifying peptide ligands from libraries that comprise large collections of peptides, ranging from 1 million to 1 billion difference sequences, which can be screened using monoclonal antibodies or target molecules. The power of this technology stems from the chemical diversity of the amino acids coupled with the

large number of sequences in a library. See for example, Scott et al., Cur. Open. Biotechnol. 5(1):40-8 (1994); Kenan et al. Trends Biochem. Sci. (1994) 19(2):57-64. Accordingly, the monoclonal antibodies, preferably human monoclonals or fragments thereof, generated as discussed herein, find use in treatment by inhibiting or treating HIV infection or disease progression, as well as in screening assays to identify additional pharmaceuticals.

Production of gp120

gp120 for a vaccine can be produced by any suitable means, as with prior art HIV gp120 subunit vaccines. Recombinantly-produced or chemically synthesized gp120 is preferable to gp120 isolated directly from HIV for safety reasons. Methods for recombinant production of gp120 are described below.

Oligonucleotides encoding gp120 from breakthrough isolates and capable of expressing gp120 can be prepared by conventional means. For example, the nucleotide sequence can be synthesized. Alternatively, another HIV nucleotide sequence encoding gp120 can be used as a backbone and altered at any differing residues as by site-directed mutagenesis. Site-directed mutagenesis is described in Kunkel et al, *Proc. Natl. Acad. Sci. (USA)* **82**:488-492 (1985) and Zoller et al, *Nuc. Acids Res.* **10**:6487-6500 (1982) and is well known.

In a preferred embodiment, the nucleotide sequence is present in an expression construct containing DNA encoding gp120 under the transcriptional and translational control of a promoter for expression of the encoded protein. The promoter can be a eukaryotic promoter for expression in a mammalian cell. In cases where one wishes to expand the promoter or produce gp120 in a prokaryotic host, the promoter can be a

prokaryotic promoter. Usually a strong promoter is employed to provide high-level transcription and expression.

The expression construct can be part of a vector capable of stable extrachromosomal maintenance in an appropriate cellular host or may be integrated into host genomes. Normally, markers are provided with the expression construct which allow for selection of a host containing the construct. The marker can be on the same or a different DNA molecule, desirably, the same DNA molecule.

The expression construct can be joined to a replication system recognized by the intended host cell. Various replication systems include viral replication systems such as those from retroviruses, simian virus, bovine papilloma virus, or the like. In addition, the construct may be joined to an amplifiable gene, e.g. the DHFR gene, so that multiple copies of the gp120 DNA can be made. Introduction of the construct into the host will vary depending on the construct and can be achieved by any convenient means. A wide variety of prokaryotic and eukaryotic hosts can be employed for expression of the proteins.

Preferably, the gp120 is expressed in mammalian cells that provide the same glycosylation and disulfide bonds as in native gp120. Expression of gp120 and fragments of gp120 in mammalian cells as fusion proteins incorporating N-terminal sequences of Herpes Simplex Virus Type 1 (HSV-1) glycoprotein D (gD-1) is described in Lasky, L. A. et al., 1986 (Neutralization of the AIDS retrovirus by antibodies to a recombinant envelope glycoprotein) Science **233**: 209-212 and Haffar, O.K. et al., 1991 (The cytoplasmic tail of HIV-1 gp160 contains regions that associate with cellular membranes.) Virol. **180**:439-441, respectively. A preferred method for expressing gp120 is described in

the examples. In the examples, a heterologous signal sequence was used for convenient expression of the protein. However, the protein can also be expressed using the native signal sequence.

An isolated, purified gp120 polypeptide having one of the amino acid sequences illustrated in Table 1 can be produced by conventional methods. For example, the proteins can be chemically synthesized. In a preferred embodiment, the proteins are expressed in mammalian cells using an expression construct of this invention. The expressed proteins can be purified by conventional means. A preferred purification procedure is described in the examples.

gp120 Fragments

The present invention also provides gp120 fragments that are suitable for use in inducing antibodies for use in a vaccine formulation. A truncated gp120 sequence, as used herein, is a fragment of gp120 that is free from a portion of the intact gp120 sequence beginning at either the amino or carboxy terminus of gp120. A truncated gp120 sequence of this invention is free from the C5 domain. The C5 domain of gp120 is a major immunogenic site of the molecule. However, antibodies to the region do not neutralize virus. Therefore, elimination of this portion of gp120 from immunogens used to induce antibodies for serotyping is advantageous.

In another embodiment, the truncated gp120 sequence is additionally free from the carboxy terminal region through about amino acid residue 453 of the gp120 V5 domain. The portion of the V5 domain remaining in the sequence provides a convenient restriction site for preparation of expression constructs. However, a truncated gp120 sequence that is free from the entire gp120 V5 domain is also

suitable for use in inducing antibodies.

In addition, portions of the amino terminus of gp120 can also be eliminated from the truncated gp120 sequence. In particular, the truncated gp120 sequence can be free from the gp120 signal sequence. The truncated gp120 sequence can be free from the carboxy terminus through amino acid residue 111 of the gp120 C1 domain, eliminating most of the C1 domain but preserving a convenient restriction site. However, the portion of the C1 domain through the V2 cysteine residue that forms a disulfide bond can additionally be removed, so that the truncated gp120 sequence is free from the carboxy terminus through amino acid residue 117 of the gp120 C1 domain. In a preferred embodiment, the truncated gp120 sequence is free from the amino terminus of gp120 through residue 111 of the C1 domain and residue 453 through the carboxy terminus of gp120.

The truncated gp120 sequences can be produced by recombinant engineering, as described previously. Conveniently, DNA encoding the truncated gp120 sequence is joined to a heterologous DNA sequence encoding a signal sequence.

It is understood that the application of the teachings of the present invention to a specific problem or situation is within the capabilities of one having ordinary skill in the art in light of the teachings contained herein. Examples of the products of the present invention and representative processes for their isolation, use, and manufacture appear below, but should not be construed to limit the invention. All literature citations herein are expressly incorporated by reference.

EXAMPLES

Materials and Methods

Specimen collecti n from human volunt ers. Blood was collected from MN-rgp120-immunized individuals who were infected with HIV-1 while participating in Phase I (NIH Protocol AVEG 016) and Phase II (NIH Protocol AVEG 201) HIV-1 vaccine trials sponsored by the National Institutes of Health (NIH). The demographics of the subjects in the study, and the study design have been described in McElrath; *Seminars in Cancer Biol.* 6:1-11 (1995); McElrath et al.; *Abstracts from Eighth Annual Meeting of the National Cooperative Vaccine Development Groups for AIDS. Bethseda, MD* 216 (1996). Specimens were obtained according to an informed consent protocol approved by the institutional review boards of the participating institutions. In the experimental section, the time of HIV-1 infection is specified with regard to data provided by the NIH AIDS Vaccine Evaluation Network where PCR (RNA) and/or serologic assays were used to detect HIV-1 infection.

Sample preparation for cloning HIV-1 envelope glycoproteins. Peripheral blood mononuclear cells (PBMCs) from HIV-1 infected vaccinees were prepared from heparinized venous blood by FICOLL-HYPAQUE gradient centrifugation. Cell number and viability were determined. After separation, PBMCs were washed twice in phosphate-buffered saline and suspended at a cell density of $6x10^6$ cells/ml in PCR lysis buffer (50 mM KCl, 10 mM Tris (pH 8.4), 2.5 mM $MgCl_2$, 0.1 mg/ml gelatin (Sigma), 0.45% NONIDET P40 detergent, 0.45% TWEEN 20 detergent (both detergents are commercially available from United States Biochemical Corp.) and 0.06 mg/ml Proteinase K (Gibco BRL) to lyse the cells. The lysate was incubated at 50-60°C for 1 hour, followed by inactivation of the Proteinase K at 95°C for 10 minutes. Lysates were shipped frozen and stored at -70°C until use.

Polymerase chain reaction (PCR) amplificati n. Samples were subjected to two rounds of PCR amplification using the nested primers described below. In the first round, 25 μl aliquots of PBMC lysates (containing about 1 μg genomic DNA) were mixed with an equal volume of a PCR reaction mix containing 400 μM each dNTP, 200 μg/ml BSA (Sigma Chemical Corporation, RIA grade) and about 100 pmoles of each primer in 50 mM KCl, 20 mM Tris (pH 8.4) and 3 mM $MgCl_2$. After an initial 10 minute denaturation step at 95°C, 5 units of *Taq* polymerase (AMPLITAQ, Perkin Elmer Cetus) were added during an 55°C soak step, and samples were overlayed with mineral oil.

The PCR profile was as follows: 2 cycles having 1 minute at 55°C, 2.5 minutes at 72°C and 1 minute at 94°C, followed by 28 cycles with 30 seconds at 55°C, 2.5 minutes at 72°C and 45 seconds at 94°C, and an extension step at 72°C for 5 minutes.

Aliquots of 10 μl from the first-round reactions were re-amplified with appropriate nested primers in a final reaction volume of 100 μl, using either the reagents and profile described above or the reagents and profile described in the PCR Optimizer Kit (Invitrogen.) PCR reaction products were purified using QIAQUICK-spin columns (Qiagen Inc.) The primer pair used in the first round was either **120.os.F** (5'-gggaattcggatccAGAGCAGAAGACAGTGGCAATGA with homologous sequence at position 6248-6270 of HIVPV22) (SEQ. ID. NO. 34) or **JM11A** (5'-ctcgag-CTCCTGAAGACAGTCAGACTCATCAAG at position 6048-6074) (SEQ. ID. NO. 35) in the forward direction [Kusumi et al.; *J. Virol.* **66**:875 (1992)] combined with **120.os.R** (5'-ggtctagaagctttaGCCCATAGTGCTTCCTGCTGCT-CC at position 7836-7859) (SEQ. ID. NO. 36) in the reverse direction. The internal nested primers were **120.BX.F** (5'-gggcggatcctcgaGGTACCTGTRTGGAAAGAAGCA at position

6389-6410; R: A or G) (SEQ. ID. NO. 37) and **120.is.R** (5'-ggtctagaagctttaTGCTCCYAAGAACCCAAGGAACA at position 7819-7841; Y: T or C) (SEQ. ID. NO. 38). Heterologous primer sequences are shown in lower case letters.

Subcloning of PCR products and the expression of recombinant envelope glycoproteins as fusion proteins. The HIV-1 envelope glycoprotein gp120 sequences were cloned and expressed as chimeric genes and fusion proteins, where the signal sequence and 27 amino acids from the mature N terminus of herpes simplex virus type 1 (HSV-1) were fused to the N-terminal sequences of the gp120 genes, corresponding to amino acid 13 of the mature gp120 sequence. PCR products containing gp120 sequences from the breakthrough specimens were cloned into pRK5 expression plasmid as chimeric genes using combinations of restrictions sites engineered into the heterologous PCR primer tails and the Xho I site engineered into the N-terminal sequence of HSV-1 gD.

The resulting double-stranded DNA was sequenced with Sequenase and the dGTP Reagent Kit (United States Biochemical Corp.). Sequences from glycoprotein D were provided to enhance expression and to provide a flag epitope to facilitate protein analysis, as described in Berman et al.; *J. Virol.* 7:4464-9 (1992); Nakamura et al.; *AIDS and Human Retroviruses* 8:1875-85 (1992); and Nakamura et al.; *J. Virol.* 67:6179-91 (1993).

Briefly, isolated DNA fragments generated by the PCR reaction were ligated into a plasmid (pRK.gD-5, pRKgDstop) designed to fuse the gp120 fragments, in frame, to the 5' sequences of the glycoprotein D (gD) gene of Type 1 Herpes Simplex Virus (gD-1)and the 3' end to translational stop codons. The fragment of the gD-1 gene encoded the signal sequence and 25 amino acids of the mature form of HSV-1 protein. To allow

for expression in mammalian cells, chimeric genes fragments were cloned into the pRK5 expression plasmid (Eaton et al., *Biochemistry* **291**:8343-8347 (1986)) that contained a polylinker with cloning sites and translational stop codons located between a cytomegalovirus promotor and a simian virus 40 virus polyadenylation site.

The resulting plasmids were transfected into the 293s embryonic human kidney cell line (Graham et al., *J. Gen. Virol.* **36**:59-77 (1977)) using a calcium phosphate technique (Graham et al., *Virology* **52**:456-467 (1973)). Growth conditioned cell culture media was collected 48 hr after transfection, and the soluble proteins were detected by ELISA or by specific radioimmunoprecipitation where metabolically labeled proteins from cell culture supernatants were resolved by sodium dodecyl sulfate polyacrylamide gel electrophoresis (PAGE) and visualized by autoradiography as described in Berman et al., *J. Virol.* **63**:3489-3498 (1989) and Laemmli, *Nature* **227**:680-685 (1970).

Serologic assays. Sera were assayed for antibodies to rgp120, antibodies to synthetic gp120 V3 domain peptides corresponding to sequences from the gp120 V3 domain, and antibodies able to inhibit the binding of MN-rgp120 to cell surface CD4 using serologic assays described in Berman et al.; *J. Virol.* **7**:4464-9 (1992); Nakamura et al.; *AIDS and Human Retroviruses* **8**:1875-85 (1992); and Nakamura et al.; *J. Virol.* **67**:6179-91 (1993). Endpoint titers of antibody binding to gp120 and V3 peptides were determined using three fold-serial dilutions of sera. The endpoint dilution titer was defined as the last dilution that produced an optical density value that was two times higher than the mean of the optical

densities of 1:50 diluted, pooled, normal human sera. Antibody titers were calculated by a computer program that interpolated values between antibody dilutions. The inter-assay coefficient of variation of positive control standard sera was 35%.

Binding of monoclonal antibodies to rgp120 from breakthrough viruses. An ELISA similar to that described by Moore et al.; *AIDS* 3:155-63 (1989) was used to measure the binding of various monoclonal antibodies (MAbs) to rgp120s from breakthrough viruses. Briefly, Nunc-Immuno plates (Maxisorp, certified) were coated (100 μl at 5 μg/ml in PBS at 4°C overnight) with an affinity-purified sheep polyclonal antiserum to a peptide at the C terminus of gp120 (D7324, International Enzymes, Fallbrook, CA). After washing once with PBS-0.05% TWEEN-20 detergent, the plates were blocked with PBS-1.0% BSA for 30-60 minutes at room temperature. Cell culture supernatants from 293s cells, diluted to contain equivalent amounts of the gD-rgp120 fusion protein, were added and incubated for 2 hours at room temperature followed by three washes with PBS-0.05% TWEEN-20 detergent. Various MAbs were diluted in PBS-1.0% BSA and 100 μL of the diluted MAbs were added to each well and incubated for 1 hour at room temperature.

The plates were washed 3 times and incubated with 100 μl of a horseradish peroxidase-conjugated second antibody (goat anti-mouse or anti-human IgG, Cappel) for 1 hour at room temperature. After 3 washes the plates were developed and the OD_{492} (optical density at 492 nm) read in a plate reader. Growth conditioned cell culture supernatants were normalized by dilution based on binding by MAb 5B6 which is specific for HSV-1 glycoprotein D fusion protein.

Virus n utralization assays. The ability of vaccinee sera to inhibit infection of MT4 cells by HIV-1_{MN} was measured in a cytopathicity assay where cell viability was quantitated using a calorimetric indicator dye, as described in Robertson et al.; *J. Virol. Methods* **20**:195-202 (1988). Briefly, a virus stock of HIV-1_{MN} (obtained from Dr. Michael Norcross, U.S. Food and Drug Administration) was prepared as the clarified supernatant from chronically infected H9/HIV-1_{MN} cell culture. H9 cells chronically infected with HIV-MN were pelleted and resuspended in one-tenth the original volume of medium. Cell-associated virus was released by the mechanical shearing effects of rapid vortexing of the cells as described in Wrin et al.; *J. Virol.* **69**:39-48 (1995).

An amount of virus sufficient to ensure complete cell lysis killing in 7 days was incubated with three-fold serial dilutions of test antisera, and then used to challenge MT4 T-lymphoid cells in 10% FCS/RPMI-1640 cell culture media. The cultures were incubated for 7 days at 37°C in 5% CO_2, and then cell viability was tested by the dye MTT, as described by Robertson et al.; *J. Virol. Methods* **20**:195-202 (1988). Virus neutralization endpoints were quantitated by measurement of OD at 570-650 nm, and then the endpoint titers were calculated as the reciprocal of the antiserum dilution giving a signal that was two-fold above the control signal with unprotected (killed) cells. These titers were typically twice those calculated at 50% protection.

Results

Immunization history of infected subjects. Since 1992, 499 adults have been immunized with MN-rgp120 in Phase I trials in low or moderate risk individuals and in a Phase II clinical trial involving moderate to high

risk individuals. The studies described herein entail the genetic and immunologic characterization of the first seven of nine individuals who became infected with HIV-1 through high risk behavior during the course of these trials. A listing of the trials and summary of the status of the vaccinees is presented in Table 2A. A listing of the analysis of the vaccinees is presented in Table 2B.

TABLE 2A

Description of Vaccinees Infected with HIV-1 After Immunization with MN-rgp120

Study No.	Case No.	*Risk Group	‡Antigen dose/ Adjuvant
016	C6	M/H	300/QS21
016	C8	M/H	600/QS21
016	C15	M/H	300/QS21
201	C7	M/H	600/Alum
201	C11	M/H	600/Alum
201	C10	M/IDU	600/Alum
201	C17	M/IDU	600/Alum

* - M/H indicates male homosexual; M/IDU indicate male intravenous drug user.

‡ - numbers indicate dose in micrograms of MN-rgp120 injected per immunization; QS21 indicates antigen was formulated in QS21 adjuvant; Alum indicates MN-rgp120 formulated in aluminum hydroxide.

TABLE 2B

Description of Vaccin s Infected with HIV-1 After Immunization with MN-rgp120

Case No.	Injection Schedule (months)	Injections before HIV-1+	Time of HIV-1+ (months)	¤Interval: to HIV-1+ (months)
C6	0,1,10.5	2	4.00	2.00
C8	0,1	2	4.00	3.00
C15	0,1,2	3	6.25	4.00
C7	0,1,6,12	3	9.25	3.00
C11	0,1,6,12	4	19.50	6.75
C10	0,1,6,19	3	19.50	13.50
C17	0,1,6,18	4	24.75	6.25

¤ - indicates interval between last immunization and detection of HIV-1 infection.

Three of the infections occurred in a Phase I trial (NIH Protocol AVEG 201) that compared the safety and immunogenicity of MN-rgp120 formulated in two different adjuvants (alum and QS21), and four of the infections occurred in a Phase II trial aimed at establishing the safety and immunogenicity of MN-rgp120 in various high risk groups (e.g., intravenous drug users, homosexual and bisexual males, and partners of HIV-1 infected individuals).

Of the seven infections studied (Table 3), two (C6 and C8) occurred after two injections, three (C7, C10 and C15) occurred after three injections, and two (C11 and C17) occurred after receiving the four scheduled injections. The interval between receiving the last immunization and becoming infected was 2 to 13.5 months.

TABLE 3

P ak Post Boost MN-rgp120 Antibody Titers in Vaccinees that Became Infected with HIV-1

Injections	C6	C8	C15	C7	C11	C10	C17
1	<50	2185	79	<50	1890	na	na
2	21539	10125	na	413	32696	7771	7056
3	#	#	4460	9707	34728	11627	18413
4	#	#	#	#	#	#	11340

- indicates specimen not analyzed because of HIV-1 infection.
na - indicates the sample was not available for testing.
boldface - indicates unusually low antibody titers.

Antibody response to gp120 in vaccinated individuals. The magnitude and specificity of the antibody response to MN-rgp120 was measured by ELISA in all infected individuals throughout the course of the immunization regime (Figure 1). Five of the seven

subjects exhibited normal antibody response kinetics that included a small but reproducible primary response (1:100-1:2,000) and a strong secondary (booster) response (titters ranging from 1:7,000-1:32,000), and antibody responses following third and fourth injections that were similar or marginally higher than those achieved after the second immunization (Figure 1, Table 3).

The antibody response observed in C7 (Figure 1C) was unusual in that no antibodies were detectable after the primary injection and a titer of only 1:350 was detected after the second injection. It thus appeared that C7 did not respond to the primary immunization, and that the antibody response obtained after the second injection represented a primary immune response. Consistent with this hypothesis, the third injection elicited a titer of only 1:9,707, typical of those normally seen after two immunizations.

An atypical antibody response was also seen in subject C15 (Figure 1G) who was immunized according to an accelerated immunization schedule of 0, 1, and 2 months. As expected, the antibody titer seen in this subject (1:4,460) was at the low end of what is typically achieved after two immunizations and was far below normal values for three immunizations. The lack of an effective booster response after the third immunization of C15 was not surprising in view of previous studies where an accelerated 0, 1, and 2 month immunization schedule in baboons [Anderson et al.; *J. Infect. Dis.* **160**:960-9 ((1989)] similarly prolonged the secondary response and failed to elicit an effective tertiary booster response.

Retrospective analysis of serum and plasma from subjects C6 (Figure 1A) and C8 (Figure 1B) indicated that they became infected with HIV-1 at some point between the second and third immunizations. Serologic

evidence of HIV-1 infection was evident in the gp120 antibody assays where the titers failed to decline two weeks after the second injection and instead formed an uncharacteristic high titer plateau (Figures 1A and 1B). A similar plateau in MN-rgp120 titer after the third injection, suggested that subject C7 became infected around week 36, approximately 16 weeks after receiving the third injection (Figure 1C). Subjects C10 (Figure 1E), C11 (Figure 1D), C15 (Figure 1G), and C17 (Figure 1F) developed unexpected increases in gp120 titers, typical of HIV-1 infection, after either the third or fourth immunizations. The data obtained demonstrate that immunologic priming for MN-rgp120 antibody responses is insufficient to provide universal protection from HIV-1 infection.

Antibody titers to the V3 domain. To further characterize the antibody response to gp120, antibody titers were measured to a synthetic V3 domain peptide of MN-rgp120 containing the principal neutralizing determinant (PND). Five of the seven subjects developed good V3 titers (1:400 to 1:4000) after the second immunization, however two subjects (C7 and C15) required three immunizations before developing significant tiers (Figures 1C and 1G). As had been observed previously (11), the peak V3 titers in some individuals (e.g. C11, C10, C17) appeared to decline with each successive immunization (Figures 1D, 1E, and 1F). After HIV-1 infection, two patterns of V3 reactivity were observed. Three subjects (C6, C7, and C10) showed large increases in titer to V3 domain peptides (Figures 1A, 1C, and 1E) whereas C8 (Figure 1B) showed a large decrease in V3 titer. At the time of analysis, the data were insufficient to

draw any conclusions regarding the changes in V3 titers in response to HIV-1 infection in subjects C11, C15 and C17.

The results obtained indicate that the ability to form antibodies reactive with the V3 domain at various time-points prior to HIV-1 infection is not a valid correlate of protective immunity against all strains of HIV-1.

CD4 Inhibition titers. Antibodies that block the binding of gp120 to CD4 represent a heterogeneous class of virus neutralizing antibodies. Some are known to bind to the C4 domain of gp120 [Nakamura et al.; *J. Virol.* **67**:6179-91 (1993); Anderson et al.; *J. Infect. Dis.* **160**:960-9 ((1989)], and some are known to recognize conformation dependent discontinuous epitopes [Berman et al.; *J. Virol.* 7:4464-9 (1992); Nakamura et al.; *J. Virol.* **67**:6179-91 (1993); McKeating et al.; *AIDS Research and Human Retroviruses* **8**:451-9 (1992); Ho et al.; *J. Virol.* **65**:489-93 (1991); Barbas et al.; *Proc. Natl. Acad. Sci. USA* **91**:3809-13 (1994)].

One way to detect antibodies to both types of epitopes is to measure the ability of vaccinee sera to prevent the binding of [^{125}I]-labeled gp120 to cell surface CD4 [[Nakamura et al.; *AIDS and Human Retroviruses* **8**1875-85 (1992); Nakamura et al.; *J. Virol.* **67**:6179-91 (1993)]. CD4 blocking titers were detected in all seven of the vaccinees prior to infection (Figure 2) with peak titers that ranged from 1:10-1:300. At the last time point prior to infection, the CD4 titers in five of the seven vaccinees was low (1:30 or less). One vaccinee (C17), however, possessed a CD4 blocking titer of about 1:300 prior to infection (Figure 2F). Thus, the lack of antibodies that block the binding of MN-rgp120 to CD4 cannot account for all

of the infections. Large increases in CD4 blocking titers (1:100-1:1,000) were seen in five of the seven subjects after HIV-1 infection. These included vaccinees C6, C7, C8, C10, and C11. These results demonstrate that the CD4 blocking titers elicited by MN-rgp120 were lower than those elicited by natural infection.

Virus neutralizing activity. The virus neutralizing activity of antisera from MN-rgp120-immunized subjects was measured using a colorimetric assay that measured the viability of MT-4 cells after incubation with antibody treated virus ($HIV\text{-}1_{MN}$). Since the actual date of infection was not known for any of the breakthrough infections, and serum samples were collected infrequently, the magnitude of the neutralizing antibody response at the time of infection is not known for any of the vaccinees.

Of the seven infections examined, the serum sample closest to the time of infection was that obtained from C7, where a neutralizing titer of 1:15 to $HIV\text{-}1_{MN}$ was present three weeks prior to detection of HIV-1 infection (Table 4). In all other cases, however, the interval between the last injection and the time of infection was 10 to 25 weeks.

TABLE 4

Neutralization Activity of Sera from Vaccines Infected with HIV-1

Week	C6	C8	C15	C7	C11	C10	C17
0	<10*	<10*	<10*	<10*	<10*	<10*	<10*
2	<10	<10	<10	-	-	-	-
4	<10*	<10*	nd*	<10*	<10*	<10*	<10*
6	10	80	-	<10	30	150	150
8	-	-	nd*	-	-	-	-
10	-	-	35	-	-	-	-
15	-	-	-	<10	-	-	-
16	150#	250#	-	-	30	10	<10
24			150#	<10*	20*	<10*	<10*
26				70	500	200	400
30				-	-	40	100
33				15	-	-	-
35				-	100	-	-
36				30#	-	10	40
52					30*	<10	<10
54					250	-	-
57					100	-	-
63					90	-	-
64					-	-	<10
77					40#	-	-
78						500#	10*
80							100
84							60

90	150
104	150#

* - indicates immunization.
\# - indicates HIV-1 positive.
nd - indicates not done.
- - indicates sample not available.

When sera from the two early infections were examined (Table 4), one individual (C6) had a peak neutralizing titer of 1:10 ten weeks prior to detection of HIV-1 infection, whereas the other individual (C8) had a neutralizing titer of 1:80 ten weeks prior to detection of HIV-1 infection. Subject C15, who was immunized according to an accelerated immunization schedule, developed a neutralizing titer of 1:35 after the third injection, 14 weeks prior to HIV-1 infection. Subject C10, who had a peak neutralizing titer of 1:200 following the third immunization (week 24), had no detectable titer at week 52, six months prior to the first indication of HIV-1 infection (week 78).

Subject C11 possessed a neutralizing titer of 1:90 at fourteen weeks prior to detection of HIV-1 and a peak titer of 1:500 following the third immunization. Similarly vaccinee C17 had a neutralizing titer of 1:150 fourteen weeks prior to infection and a peak titer of 1:400 at two weeks after the third immunization.

Based on the rate of decay of the gp120 response of approximately two months [Belshe et al.; *JAMA* **272(6)**:475-80 (1994)], as well as the observation that neutralizing titers of 1:150 decayed to 1:10 in 10 weeks in vaccinees C10 and C17, it appears that neutralizing titers in C8, C15, C11, and C17 could have declined to 1:10 or less in the intervals between the last pre-infection serum sample and the time of HIV-1

detection.

The results of these studies demonstrated that all vaccinees developed some level of virus-neutralizing antibodies at some time prior to HIV-1 infection, and that the magnitude of the neutralizing response was probably low at the time of infection. In general, the magnitude of the virus-neutralizing response observed in the individuals that became infected with HIV-1 was comparable to that seen in non-infected vaccinees as described in Belshe et al.; *JAMA* 272(6):475-80 (1994).

Sequences of Viruses. To evaluate the similarity of the breakthrough viruses with the vaccine antigen, nucleotide sequences for gp120 from all seven breakthrough viruses were determined. Envelope glycoprotein genes were amplified from proviral DNA using the polymerase chain reaction. Sequences were obtained by direct amplification of DNA from lysates of gradient-purified lymphocytes obtained directly from patient blood without any intermediate tissue culture or amplification step.

A listing of the complete gp120 sequences (two clones per specimen) is provided in Figure 3. All seven envelope glycoproteins possessed sequences typical of subtype (clade) B viruses. The overall homology with MN-rgp120 ranged from 69-80% (Table 5).

TABLE 5

Comparison of MN-rgp120 Sequence with Sequences from Infected Vaccinees*

	MN	C6.1	C8.3	C7.2	C11.5	C10.5	C17.1	C15.2
MN	100	79	78	70	75	69	80	72
C6.1		100	78	70	81	75	90	79
C8.3			100	68	80	76	84	83
C7.2				100	80	73	76	73
C11.5					100	75	70	80
C10.5						100	70	72
C17.1							100	87
C15.2								100

* - Data indicate percent identity.

Interestingly, a high percentage (four of seven) of the breakthrough viruses differed from MN-rgp120 by 25-30% [Myers et al.; *Retroviruses and AIDS Database, Los Alamos National Laboratory* (1992 and 1995)]. Historically this degree of sequence variation is typical of inter-subtype (intra-clade) variation rather than intra-subtype variation which is expected to be in the 10-20% range [Myers et al.; *Retroviruses and AIDS Database, Los Alamos National Laboratory* (1992 and 19950]. Of the viruses with the greatest homology to MN-rgp120, two (C6 and C8) occurred as early infections, prior to complete immunization, and one (C17) occurred as a late infection.

Polymorphism in the V3 Domain. Of particular interest were polymorphisms in regions known to contain epitopes recognized by virus neutralizing antibodies. The best characterized neutralizing epitope, the principal neutralizing determinant (PND), occurs at the

tip of the V3 loop. In subtype B viruses, approximately 60% possess the MN serotype-defining signature sequence, IGPGRAF (SEQ. ID. NO. 39), based on identity with the prototypic MN strain of HIV-1 [Berman et al.; *J. Virol.* 7:4464-9 (1992); Myers et al.; *Retroviruses and AIDS Database, Los Alamos National Laboratory* (1992 and 1995); La Rosa et al.; *Science* **249**:932-5 (1990)].

Three of the viruses (C6, C8, and C17) possessed the MN serotype signature sequence (Figure 3). In contrast, four viruses possessed sequences with radical amino acid substitutions in the PND [IGPGRAW (C7), LGPGSTF (C11), IGPGRVL (C10), and IGPGSAF (C15)] (SEQ. ID. NOs. 40-43, respectively), and therefore were classified as "non-MN like" viruses. Of note, each of the four "non-MN-like" sequences were rare (Table 6) and were not typical of the most common "non-MN" variants of subtype B viruses [Myers et al.; *Retroviruses and AIDS Database, Los Alamos National Laboratory* (1992 and 1995)].

TABLE 6

Frequency of Polymorphisms at the Principal Neutralizing Determinant in HIV-1 Infected Individuals Immunized with MN-rgp120*

V3 Sequence		Observed	Dataset Frequency			
Sequence	n	Frequency	GNE (n=52)	LANL (n=519)	LANL.1 (n=160)	LaRosa (n=245)
GPGRAF	3	0.42	0.67	0.57	0.66	0.60
GPGRAW	1	0.14	0.03	0.013	0.06	0.010
GPGRVL	1	0.14	<0.02	0.004	<0.006	<0.008
GPGSTF**	1	0.14	<0.02	<0.002	<0.006	<0.004
GPGSAF	1	0.14	0.02	0.011	<0.006	<0.004

* - Data set GNE refers to a collection of 52 independent isolates collected in 1992; dataset LANL refers to a collection of 519 sequences reported by Myers et al., Retroviruses and AIDS Database, Los Alamos National Laboratory 1992 and 1995; LANL.1 refers to a collection of 160 epidemiologically unlinked individuals provided by B. Korber (personal communication); dataset La Rosa refers to sequence data reported by La Rosa et al., *Science* **249**:932-5 (1990).

** - Sequences were not present in the data sets examined.

The prevalence of viruses with PND sequences matching the breakthrough viruses ranged from a high of 1.3% (C7) to a low of 0.2% (C11) in a listing of 519 subtype B sequences compiled by the Los Alamos National Laboratory [Myers et al.; *Retroviruses and AIDS Database, Los Alamos National Laboratory* (1992 and 1995)]. Similarly low frequencies were observed in

three other independently derived data sets (Table 6). The occurrence of these sequences did not differ significantly between data sets collected prior to 1985 [La Rosa et al.; *Science* **249**:932-5 (1990)] and data collected 1992, or from a set of 160 epidemiologically unlinked individuals (B. Korber, personal communication). All four sets of data agreed that the prevalence of viruses with MN-like PND sequences was in the range of 60%. Based on this data, four of the seven breakthrough infections were determined to be caused by viruses that fell outside of the spectrum of viruses that the vaccine was expected to prevent.

Other features of breakthrough virus V3 domains. Like MN-rgp120, the V3 domains of all of the breakthrough viruses were 36 amino acids in length. However, all seven viruses differed from MN-rgp120 with respect to the number of glycosylation sites and with respect to the syncytium-inducing (SI) signature sequence.

The sequence of MN-rgp120 is somewhat unusual [Myers et al.; *Retroviruses and AIDS Database, Los Alamos National Laboratory* (1992 and 1995)] in that it lacks an N-linked glycosylation site at position 306 in the V3 domain. The lack of this glycosylation site does not appear to be antigenically significant since antisera to MN-rgp120 are known to neutralize a variety of viruses (e.g. SF-2, DU6587-5, DU4489-5, CC) that possess a glycosylation site at this position [Berman et al.; *J. Virol.* 7:4464-9 (1992)]

In addition, the V3 domain of MN-rgp120 possessed sequence polymorphisms (R at position 311, K at position 324, K at position 328) typical of syncytium inducing viruses [Fouchier et al.; *J. Virol.* **66**:3183-87 (1992)], whereas all seven breakthrough viruses possessed sequences associated with non-syncytium-

inducing viruses. Syncytium-inducing viruses have been associated with rapid disease progression [Tersmette et al.; *J. Virol.* **62**:2026-32 (1988)] and T cell tropism [O'Brien et al.; *Nature (London)* **348**:69-73 (1990); Shioda et al.; *Nature (London)* **349**:167-9 (1991)]. To date viruses with these properties have not been recovered from any of the MN-rgp120 immunized volunteers.

Polymorphism in the V1, V2 and C4 domains. Previous investigations have identified additional neutralizing epitopes in the V1, V2 and C4 domains of gp120 [Nakamura et al.; *J. Virol.* **67**:6179-91 (1993); McKeating et al.; *AIDS Research and Human Retroviruses* **8**:451-9 (1992); Ho et al.; *J. Virol.* **65**:489-93 (1991); Barbas et al.; *Proc. Natl. Acad. Sci. USA* **91**:3809-13 (1994); McKeating et al.; *J. Virol.* **67**:4932-44 (1993); Moore et al.; *J. Virol.* **67**:6136-6151 (1993); Davis et al.; *J. Gen. Virol.* **74**:2609-17 (1993)].

The best characterized of these neutralizing epitopes is in the C4 domain which has attracted special attention because antibodies binding to this area are known to block the binding of gp120 to CD4 [Moore et al.; *AIDS* 3:155-63 (1989); McKeating et al.; *AIDS Research and Human Retroviruses* **8**:451-9 (1992)]. Because the epitope is located in a conserved (C) domain, naturally-occurring polymorphism in this region is far more limited than in other neutralizing epitopes. Nakamura et al.; *J. Virol.* **67**:6179-91 (1993) reported that the binding of a number of neutralizing MAbs was dependent on K at position 429.

Comparison of the sequence of MN-rgp120 with other strains of HIV-1 showed that a common polymorphism, involving the substitution of E for K, occurs at this position. Indeed, substrains of the same virus isolate often show polymorphism at this position. The HXB2

substrain of HIV-1_{LAI} contains K at position 429, whereas the BH10, IIIB, and LAV substrains of the HIV-1_{LAI} contain E at this position [Nakamura et al.; *J. Virol.* **67**:6179-91 (1993)]. Similarly, the 1984 isolate of HIV-1_{MN} exhibited E at this position, while the 1990 isolate of HIV-1_{MN}, used to produce MN-rgp120, possessed K at this position.

When the sequences of the infected vaccine recipients were examined (Figure 3), the virus from subject C17, like MN-rgp120 contained K at position 429, whereas the six other viruses that differed from the vaccine immunogen possessed E at this position. These results demonstrated that six of the seven breakthrough viruses differed from the vaccine immunogen at the CD4-blocking, neutralizing epitope in the C4 domain of gp120.

Studies with monoclonal antibodies have defined neutralizing epitopes in the V1 and V2 domains of gp120 [McKeating et al.; *J. Virol.* **67**:4932-44 (1993); Moore et al.; *J. Virol.* **67**:6136-6151 (1993); Davis et al.; *J. Gen. Virol.* **74**:2609-17 (1993)]. Like the polymorphisms that occur in the C4 domain, the V2 domains exhibit several common polymorphisms that affect the binding of virus neutralizing antibodies. One such polymorphism occurs at position 171 which is critically important for the binding of murine MAb 1025, whereas residue 187 is important for the binding of MAb several MAbs represented by 1088.

When the V2 domain sequences were examined (Figure 3), all of the infected-vaccinee viruses differed from MN-rgp120 in that R replaced G at position 171 and I or V replaced E at position 187. Antibodies recognizing these adjacent sites in the V2 domain of MN-rgp120 would not be expected to neutralize viruses with radical amino acid substitutions at these position. Thus, all seven

breakthrough viruses differed from MN-rgp120 at a neutralizing epitope in the V2 domain of gp120.

Other neutralizing epitopes have been reported in the V1 domain of gp120 [O'Brien et al.; *Nature (London)* **348**:69-73 (1990); McKeating et al.; *J. Virol.* **67**:4932-44 (1993)]. Although the neutralizing epitopes in the V1 domain of MN-rgp120 have not been characterized, the polymorphism seen among the breakthrough viruses in this region was interesting. Particularly striking (Figure 3) was that the length of this domain ranged from 20 amino acids (C17) to 45 amino acids (C6), and the number of N-linked glycosylation sites ranged from 2 to 6. In contrast, the V1 domain of MN-rgp120 is 31 amino acids in length and encodes three N-linked glycosylation sites.

Although examination of sequence databases suggest that variation in the V2 region is comparable to the V1 region, the V2 region of the breakthrough viruses showed less variation than expected. Specifically, the length of the V2 region ranged from 36 amino acids (C7) to 39 amino acids in length, with six of seven viruses containing three N-linked glycosylation sites in this domain. A high degree of polymorphism was found in the V4 region where sequences ranged from 26 (C10) to 33 (C15, C7) amino acids in length and contained either 4 or 5 N-linked glycosylation sites.

Antigenicity of envelope glycoproteins from breakthrough viruses. To determine the significance of sequence variation on glycoprotein antigenicity, recombinant gp120 was prepared from the viruses of all seven infected vaccinees (Figure 4). In these studies a series of MAbs was assembled and their binding to MN-rgp120 was compared to that of rgp120 from the vaccinee isolates by ELISA (Table 7).

TABLE 7
Relative Reactivity of MAb Binding to rgp120 fr m Infected Subj cts Compared with Binding to MN-rgp120

	V3		Discontinuous		C8	V2
gp120	1034	50.1	1.5E	1025	1024	1088
MN	1.0	1.00	1.00	1.00	1.00	1.00
C6.1	0.37	0.37	0.17	0.00	0.00	0.00
C6.5	0.33	0.33	0.75	0.00	0.00	0.00
C8.3	0.11	0.37	0.38	0.00	0.00	0.00
C8.6	0.14	0.34	0.29	0.00	0.00	0.00
C7.2	0.47	0.60	0.71	0.00	0.00	0.00
C11.5	0.00	0.00	0.17	0.00	0.00	0.00
C11.7	0.00	0.00	0.17	0.00	0.00	0.00
C10.5	0.33	0.40	0.46	0.24	0.03	0.04
C10.7	0.42	0.48	0.50	0.29	0.07	0.09
C17.1	0.33	0.52	0.33	0.00	0.30	0.07
C17.3	0.37	0.56	0.33	0.00	0.38	0.06
C15.2	0.00	0.47	0.92	0.00	0.00	0.00
C15.3	0.00	0.37	0.63	0.00	0.00	0.00

* - Relative reactivity values represent ratio of optical densities obtained with rgp120 from patient isolates divided by optical density obtained for MN-rgp120 at a MAb concentration of 2 micrograms per milliliter.

In control experiments, the binding of MAb 5B6 (which is specific for the HSV gD-1 flag epitope fused to the N terminus of all of the rgp120 protein) was used to standardize the amount of gp120 from each isolate (Figure 5A). These studies demonstrated that the assay was carried out under conditions where equivalent amount of rgp120s were captured onto wells of microtiter plates.

The antigenic structure of the V3 domain was examined using the 1034 MAb (isolated from mice immunized with MN-rgp120 as described in Nakamura et al.; *J. Virol.* 67:6179-91 (1993) and the 50.1 MAb (prepared from mice immunized with a synthetic V3 domain peptide as described in Rini et al.; *Proc.*

Natl. Acad. Sci. USA 90:6325-9 (1993). Both MAbs are known to exhibit potent virus neutralizing activity. When binding to the recombinant proteins was examined, the MAb binding to MN-rgp120 was at least 10-fold greater than to any of the breakthrough virus envelope proteins (Figure 5 B and C). Surprisingly, rgp120 from the three patient isolates (C8, C6, and C17) that possessed the MN serotype-defining sequence, IGPGRAF (SEQ. ID. NO. 39), varied from one another in their MAb binding activity. Thus, the binding of MAb 1034 and MAb 50.1 to rgp120 from C17 was significantly greater than the binding to rgp120s from C6 and C8.

A distinction in the epitopes recognized by these MAbs was evident since C6-rgp120 and C8-rgp120 gave comparable binding with 50.1, whereas 1034 bound better to the C6-derived protein than the C8-derived protein. The poorest MAb reactivity was with rgp120s from C11 and C15. This result was consistent with sequence analysis demonstrating that these two viruses both possessed the radical substitution of S for R at position 18 in the V3 domain. Surprisingly, both of these MAbs exhibited better than expected binding to rgp120 from the C7 and C10 viruses. Like MN-rgp120, both proteins contained the penta-peptide, IGPGR sequence (SEQ. ID. NO. 44) in the V3 loop, but differed from MN-rgp120 in that V and L replaced A and F at positions 319 and 320 in gp120 from C10, and W replaced F at position 320 in gp120 from C7. These results indicate that R at position 318 is essential for the binding of these two MAbs, and that the epitopes recognized by 1034 and 50.1 are not completely destroyed by the hydrophobic substitutions at positions 319 and 320.

As predicted from the sequence data, there was little if any binding to the breakthrough virus rgp120s using MAbs (1088 and 1025) directed to the V2 region of

MN-rgp120. Also consistent with sequence data was the observation that MAb 1024 directed to the C4 domain of MN-rgp120 gave some reactivity with C17-rgp120 which, like MN-rgp120 contained K at position 429, but gave no reactivity with the other isolates that contained E at residue 429.

Together, these studies demonstrated that the antigenic structure of all seven breakthrough viruses differed from the vaccine immunogen at three well characterized neutralizing epitopes.

A totally different pattern of reactivity was observed with the human hybridoma, MAb 15e, prepared from an HIV-1 infected individual as described in Ho et al.; *J. Virol.* **65**:489-93 (1991). With this MAb, the greatest binding was achieved with MN-rgp120 and rgp120 from C7, and the poorest reactivity was seen with the two clones of rgp120 from the C11. Moderate, but comparable reactivity was seen with rgp120s from the C10 and C17.

These results demonstrate that the 15e epitope is polymorphic, and that the epitope is conserved on MN-rgp120 and rgp120 from C7, but has been lost on rgp120s from C11. Interestingly, the two different clones of gp120 derived from C6 gave strikingly different patterns of antibody binding. Thus, rgp120 from clone C6.5 exhibited strong reactivity with this antibody, whereas rgp120 from clones C6.1 exhibited significantly weaker activity with this MAb. Comparison of sequence data (Figure 3) showed that the two C6 clones differed at 6 amino acid positions. Based on comparative binding to the other viral proteins of known sequence, it appeared that the substitution of K for I at position 351 in the C3 domain of gp120 could account for the difference in binding activity. This result is also consistent with both clones of C11 similarly containing a positively-

charged K at this position, and also being poorly reactive with this MAb. Alternatively, a T for I substitution at position 439 in the C4 domain could account for the difference in 15e binding between C6.1 and C6.5. Although the inability of the two C11 clones to bind 15e cannot be explained by polymorphism at this position in the C4 domain, they could be affected by the adjacent T for M substitution at position 434.

Discussion

In these studies, the viruses and immune responses in seven of nine vaccinees who became infected with HIV-1 through high risk activity while participating in Phase I or Phase 2 trials of MN-rgp120, a candidate HIV-1 vaccine were analyzed. Such infections would be expected to occur for one of two reasons: 1) lack of sufficient immune response at the time of infection; or 2) infection with viruses that fall outside of the antigenic spectrum expected to be covered by the vaccine immunogen. The data indicate that both explanations may be involved with the infections observed (Table 8).

TABLE 8

Summary of Breakthrough Infecti ns

				Homologous to MN-rgp120		
Case No.	Adequate Immunization	MN-rgp120 Homology (%)	V3 PND	C4 Epitope	V2 Epitope
C6	-	79	+	-	-
C8	-	78	+	-	-
C15	-	72	-	-	-
C7	-	70	-	-	-
C11	+	75	-	-	-
C10	+	69	-	-	-
C17	+	80	+	+	-

Two of the infections occurred in individuals who failed to receive the minimum three doses of vaccine typically required for the induction of protective immunity with protein subunit vaccines (e.g. hepatitis B virus formulated in alum adjuvant as described in Francis et al.; *Ann. Int. Med.* 97:362-6 (1982). Two additional breakthrough infections occurred in vaccinees who had weak or undetectable primary (C7) and booster (C15) responses. Of the three individuals who became infected with HIV-1 after receiving three or more productive immunizations (C10, C11, and C17), at least two, and possibly all three, appear to have become infected more than six months after receiving their last immunization. Because antibody titers to MN-rgp120 typically decay with a half-time of 2 to 2.5 months [Belshe et al.; *JAMA* 272(6):475-80 (1994); Berman et al.; *AIDS* 8:591-601 (1994)], antibody titers would be expected to have decayed at least eight-fold and possibly as much as sixty four-fold at the time of infection. Thus, the lack of a sufficient immune

response at the time of infection represents a potential explanation for at least six of the seven breakthrough infections.

Data from vaccine efficacy studies in gp160 immunized chimpanzees [McElrath et al.; Longitudinal Vaccine-Induced Immunity and Risk Behavior of Study Participants in AVEG Phase II Protocol 201. In: Abstracts from Eighth Annual Meeting of the National Cooperative Vaccine Development Groups for AIDS. Bethseda, MD 1996:216] challenged with HIV-1, and gp120-immunized rhesus macaques challenged with a chimeric SIV/HIV-1 virus (SHIV) suggest that the magnitude of the neutralizing antibody response at the time of infection is a critical correlate of protective immunity. If maintaining neutralizing antibody titers proves to be a valid correlate of protective immunity in humans, then formulations (e.g. novel adjuvants) or immunization regimes (frequent boosting) designed to maximize the antibody responses may be required to achieve long lasting protection. Use of a booster every six months may be advantageous.

The other likely explanation for the late infections is the antigenic difference between the vaccine and the breakthrough virus envelope glycoproteins. This explanation is supported by the observation that four of the seven breakthrough viruses possessed envelope glycoproteins that differed from the MN-rgp120 by 25-30% at the amino acid level. Differences of this magnitude have historically [Myers et al.; *Retroviruses and AIDS Database, Los Alamos National Laboratory* (1992 and 1995)] been associated with inter-subtype variation and far exceeds the average 10-20% variation expected for viruses within the same subtype.

Although the biologic significance of sequence variation in many regions of the envelope glycoprotein

is unclear, polymorphism at neutralizing epitopes is an important factor that affects vaccine efficacy. Previous studies [Salmon-Ceron et al.; *AIDS Res. and Human Retroviruses* **11**:1479-86 (1995); Javaherian et al.; *Science* **250**:1590-3 (1990)] have demonstrated that the breadth of neutralizing activity that could be elicited by HIV-1 envelope derived vaccines was critically dependent on the sequence of epitopes in the V3 domain (e.g.; the PND). Thus, candidate vaccines based on the LAI strain of HIV-1 (the prototypic "non-MN-like" subtype B virus), exhibited little or no cross neutralizing activity with subtype B viruses, whereas vaccines that contained the "MN-like-" PND sequence (IGPGRAF) (SEQ. ID. NO. 44) exhibited broad cross neutralizing activity. That four of the seven breakthrough viruses possessed envelope glycoproteins with radical amino acid substitutions in the PND is consistent with the explanation that differences in antigenic structure explain some of these infections.

Over the last few years, it has become clear that polymorphism among "MN-like" viruses occurs at neutralizing epitopes outside of the PND. The best example occurs in the C4 domain where two antigenically distinct variants are distinguished by the presence of either K or E at position 429 [Moore et al.; *AIDS* 3:155-63 (1989)]. Because six of the seven breakthrough viruses differed from the vaccine strain in that they contained E rather than K at position 429, antibodies raised to the C4 domain of MN-rgp120 were unlikely to neutralize the viruses infecting in six of the seven vaccinees.

Other neutralizing epitopes are known to be present in the V1 and V2 domains of gp120. Although these regions are highly variable, due to insertions and deletions, neutralizing epitopes have been described by McKeating et al.; *J. Virol.* **67**:4932-44

(1993); Moore et al.; *J. Virol.* 67:6136-6151 (1993); and Davis et al.; *J. Gen. Virol.* 74:2609-17 (1993). Several of these epitopes overlap an amino terminal sequence of the V2 domain containing the tri-peptide sequence RDK at positions corresponding to 142 to 144 of MN-rgp120 [McKeating et al.; *J. Virol.* 67:4932-44 (1993); Moore et al.; *J. Virol.* 67:6136-6151 (1993)]. Like the C4 epitope, variation in this sequence is known to occur between different substrains derived from the same parental isolate. Since all seven breakthrough viruses differed from MN-rgp120 in that they possessed the RDK sequence, rather than the GDK sequence present in the vaccine antigen, neutralizing antibodies to the V2 domain of MN-rgp120 would not have been expected neutralize any of the viruses recovered from the vaccinees immunized with MN-rgp120.

Although polymorphisms at neutralizing epitopes might account for the lack of protection in most of the infections, this does not appear to explain the infection of vaccinee C17, who was infected by a virus that matched MN-rgp120 in the V3 and C4 domains. If a difference in sequence was responsible for the lack of protection in this case, the critical difference might relate to the unusual sequence in the V1 domain of gp120 from this breakthrough virus. Several studies have shown that the V1 domain possesses epitopes recognized by virus neutralizing monoclonal antibodies [McKeating et al.; *J. Virol.* 67:4932-44 (1993); Davis et al.; *J. Gen. Virol.* 74:2609-17 (1993); Kayman et al.; *J. Virol.* 68:400-410 (1994)].

Although far less is known about the V1 epitopes relative to other neutralizing sites, the V1 epitopes appear to be conformation-dependent, and antisera from HIV-1 infected individuals recognize epitopes in the V1 and V2 domains [McKeating et al.; *J. Virol.* 67:4932-44 (1993); Kayman et al.; *J. Virol.* 68:400-410 (1994)].

The V1 sequence of the virus from C17 is noteworthy because it is smaller and contains fewer N-linked glycosylation sites than that of MN-rgp120 or any of the other breakthrough viruses. By the same token, the envelope glycoproteins from C11 and C6 are noteworthy because they are significantly larger and contain more glycosylation sites than MN-rgp120 or the other breakthrough viruses.

While differences in amino acid sequence can provide clues to differences in antigenic structure, the consequences of such polymorphism can only be proven through antibody binding studies. To correlate differences in sequence with differences in antigenic structure, gp120 from two clones each of all seven breakthrough viruses was expressed and the antigenicity of the clones with a panel of monoclonal antibodies was examined. As predicted from the sequence data, none of the breakthrough virus envelope glycoproteins reacted with neutralizing MAbs to the V2 domain of MN-rgp120. When MAbs to the C4 domain were examined, only the C17 envelope glycoprotein (that matched MN-rgp120 with respect to K429) showed significant, albeit lower, binding. Surprisingly, the three breakthrough envelope glycoproteins that contained the subtype B PND consensus sequence, IGPGRAF (SEQ. ID. NO. !!), gave poor reactivity with all three PND directed MAbs, even though they possessed PND sequences closely related to the vaccine immunogen. Thus, all three of the vaccinee isolates appeared to possess changes outside of the recognition site that interfered with MAb binding.

It has been known for many years that resistance to neutralization in vitro can sometimes be attributed to mutations in remote sequences that alter the conformation of neutralizing epitopes and interfere with recognition by virus neutralizing antibodies [Nara et al.; *J. Virol.* 64:3779-91 (1990); Cordonnier

et al.; *Nature* **340**:571-4 (1989)]. Together, these results indicate that the antigenic structure of the envelope glycoproteins recovered from the breakthrough viruses differed significantly from that of the vaccine antigen.

A novel result was the localization of residues in the C3 domain that appeared to affect the binding of the virus neutralizing human MAb, 15e. This MAb is known to recognize a discontinuous epitope, block CD4 binding, and neutralize a variety of laboratory and primary isolates of HIV-1 [Ho et al.; *J. Virol.* **65**:489-93 (1991); Thali et al.; *J. Virol.* **66**:5635-5641 (1992); Moore et al.; *AIDS Res. Hum. Retroviruses* **9**:1179-1187 (1993)].

Comparative binding to envelope glycoproteins from the breakthrough viruses indicated that recognition by this antibody is critically dependent on residues in the C3 or C4 domains of gp120. The unique occurrence of a positively charged K at position 351 in the C3 domain provides a common explanation for the inability of the C11.5, C11.7 and C6.1 strains of HIV-1 to bind to 15e. Alternatively, it is possible that different amino acid substitutions in different locations account for the failure of 15e to bind to rgp120s from the C6 and C11 clones. The only obvious positions where substitutions of this type occur are in the C4 domain where T replaces M at 434 (C11) and T replaces I at 439.

The present studies demonstrate that the current formulation of MN-rgp120 is less than 100% effective against HIV-1 infection. Based on previous in vitro and in vivo studies with MN-rgp120, protection from natural HIV-1 infection in humans is expected to depend on a threshold concentration of virus-neutralizing antibodies, and antigenic similarity between the vaccine immunogen and the challenge virus.

In this regard, only one of the seven breakthrough infections (C17) was unexpected. This individual received a full course of immunizations yet became infected with a virus similar to MN-rgp120 at at least two important neutralizing epitopes (V3 and C4 domains). This infection might be related to the magnitude of the antibody response at the time of infection, or antigenic differences between the breakthrough virus and the vaccine strain, or circumstances of infection (e.g., ulcerative lesions, infection by donor with acute infection or high viremia), not monitored in this protocol. Alternatively this individual may represent a true vaccine failure, without clear explanation.

On balance, the analysis of breakthrough infections described herein did not uncover any data that would discourage the continued development of MN-rgp120 as a vaccine to prevent HIV-1 infection. The results support speculation that enhancing vaccine immunogenicity (as by additional booster immunizations) may be required to maintain long term protective immunity, and that the addition of rgp120 from other antigenically different strains of virus in addition to MN-rgp120 are useful to expand the breadth of protection.

The availability of viruses and viral glycoproteins derived from breakthrough infections may provide an important means to streamline the process of identifying new antigens for inclusion into a multivalent vaccine. Recombinant viral glycoproteins prepared from breakthrough viruses, by definition, possess antigenic structures that are significantly different from MN-rgp120, and are be representative of viruses currently being transmitted. Thus, combining rgp120 from breakthrough viruses with MN-rgp120 is an effective way complement and significantly expand

antigenic complexity and increase breadth of cross neutralizing activity.

SEQUENCE LISTING

(1) GENERAL INFORMATION:
(i) APPLICANT: Berman, Phillip W.
(ii) TITLE OF INVENTION: HIV ENVELOPE POLYPEPTIDES AND VACCINE
(iii) NUMBER OF SEQUENCES: 44
(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: SKJERVEN, MORRILL, MACPHERSON, ET AL.
(B) STREET: 25 Metro Drive, Suite 700
(C) CITY: San Jose
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 95110
(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: WinPatin (Genentech)
(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:
(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Terlizzi, Laura
(B) REGISTRATION NUMBER: 31,307
(C) REFERENCE/DOCKET NUMBER: M-3897 US
(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (408) 453-9200
(B) TELEFAX: (408) 453-7979

(2) INFORMATION FOR SEQ ID NO:1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1503 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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GGG GTA CCT GTG TGG AAG GAA GCA ACC ACC ACT CTA 36
Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
 1               5                  10

TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
        15                  20                  25

CAT AAT GTT TGG GCC ACA CAT GCT TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
                30                  35

CCA AAC CCA CAA GAA ATG GTA TTG GAA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Met Val Leu Glu Asn Val Thr Glu
    40                  45                  50

GAT TTT AAC ATG TGG AAA AAT GAC ATG GTA GAA CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Asp Met Val Glu Gln Met
            55                  60

CAT GAG GAT ATA ATC AGT TTA TGG GAT CAA AGC CTA AAA 231
His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys
 65                  70                  75
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CCA TGT GTA AAA TTA ACC CCA CTC TGT ATT ACT TTA AAT 270
Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
        80                  85                  90

TGC ACC AAT TGG AAG AAG AAT GAT ACT AAA ACT AAT AGT 309
Cys Thr Asn Trp Lys Lys Asn Asp Thr Lys Thr Asn Ser
                95                 100

AGT AGT ACT ACA ACT AAT AAT AGT AGT GCT ACA GCT AAT 348
Ser Ser Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn
    105                 110                 115

AGT AGT AGT ACT ACA ACT AAT AGT AGT TGG GGA GAG ATA 387
Ser Ser Ser Thr Thr Thr Asn Ser Ser Trp Gly Glu Ile
            120                 125

AAG GAG GGA GAA ATA AAG AAC TGC TCT TTC AAT ATC ACC 426
Lys Glu Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr
130                 135                 140

ACA AGC ATA AGA GAC AAG GTG AAG AAA GAA TAT GCA CTT 465
Thr Ser Ile Arg Asp Lys Val Lys Lys Glu Tyr Ala Leu
        145                 150                 155

TTT TAT AGC CTT GAT GTA GTA CCA ATA GAA AAT GAT AAT 504
Phe Tyr Ser Leu Asp Val Val Pro Ile Glu Asn Asp Asn
                160                 165

ACT AGC TAT AGG TTG AGA AGT TGT AAC ACC TCA GTC ATT 543
Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val Ile
    170                 175                 180

ACA CAA GCC TGT CCA AAG GTA ACT TTT GAG CCA ATT CCC 582
Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro
            185                 190

ATA CAT TAT TGT ACC CCG GCT GGT TTT GCG ATT CTG AAG 621
Ile His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys
195                 200                 205

TGT AGA GAT AAA AAG TTC AAT GGA ACA GGA CCA TGC AAA 660
Cys Arg Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys
        210                 215                 220

AAT GTT AGC ACA GTA CAA TGT GCA CAT GGA ATT AAG CCA 699
Asn Val Ser Thr Val Gln Cys Ala His Gly Ile Lys Pro
                225                 230

GTA GTG TCA ACT CAA CTG CTG TTA AAT GGC AGC CTA GCA 738
Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
    235                 240                 245

GAA GAA GAG GTA ATA ATT AGA TCT GCC AAT TTC TCA AAC 777
Glu Glu Glu Val Ile Ile Arg Ser Ala Asn Phe Ser Asn
            250                 255

AAT GCT AAA ATC ATA ATA GTA CAG TTG AGG GAA CCT GTA 816
Asn Ala Lys Ile Ile Ile Val Gln Leu Arg Glu Pro Val
260                 265                 270

GAA ATT AAT TGT ACA AGA CCC AGC AAC AAT ACA ATA AAA 855
Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
        275                 280                 285
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GGT ATA CAC ATA GGA CCA GGG AGA GCA TTT TAT GCA ACA 894
Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr
            290                 295

GGA GAC ATA CGA GGA GAT ATA AGA CAA GCA CAT TGT AAC 933
Gly Asp Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn
    300                 305                 310

ATT AGT GGA GCA AAA TGG AAT AAC ACT TTA AAG AAG GTA 972
Ile Ser Gly Ala Lys Trp Asn Asn Thr Leu Lys Lys Val
            315                 320

GTT AAA AAA TTA AAA GAA CAA TTT CCA AAT AAA ACA ATA 1011
Val Lys Lys Leu Lys Glu Gln Phe Pro Asn Lys Thr Ile
325                 330                 335

GTC TTT AAC CAT TCC TCA GGA GGG GAC CCA GAA ATT GTA 1050
Val Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val
        340                 345                 350

ATG CAC AGT TTT AAT TGT CAA GGG GAA TTT TTC TAC TGT 1089
Met His Ser Phe Asn Cys Gln Gly Glu Phe Phe Tyr Cys
            355                 360

AAT ACA ACA AAG CTG TTT AAT AGT ACT TGG AAT GAT ACT 1128
Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp Thr
    365                 370                 375

ACA GAG TCA AAT AAC AAT GAT AGT ACT ATT ACA CTC CCA 1167
Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro
            380                 385

TGC AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA ATA 1206
Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Ile
390                 395                 400

GGA AAA GCA ATG TAT GCC CCT CCC ACC AGA GGA GAA ATT 1245
Gly Lys Ala Met Tyr Ala Pro Pro Thr Arg Gly Glu Ile
        405                 410                 415

AAA TGT TCA TCA AAT ATT ACA GGA CTA CTG TTA ATA AGA 1284
Lys Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Ile Arg
            420                 425

GAT GGT GGT ATT AAC ACT AGC GAT GCC ACC GAG ACC TTC 1323
Asp Gly Gly Ile Asn Thr Ser Asp Ala Thr Glu Thr Phe
    430                 435                 440

AGA CCG GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT 1362
Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser
            445                 450

GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA 1401
Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
455                 460                 465

GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG 1440
Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
        470                 475                 480

AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT 1479
Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu
            485                 490
```

GGG TTC TTA GGA GCA TAA AGC TTC 1503
Gly Phe Leu Gly Ala Xaa Ser Phe
495 500 501

(2) INFORMATION FOR SEQ ID NO:2:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 501 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala
1 5 10 15

Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala
20 25 30

Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Met Val
35 40 45

Leu Glu Asn Val Thr Glu Asp Phe Asn Met Trp Lys Asn Asp Met
50 55 60

Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser
65 70 75

Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
80 85 90

Cys Thr Asn Trp Lys Lys Asn Asp Thr Lys Thr Asn Ser Ser Ser
95 100 105

Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn Ser Ser Ser Thr
110 115 120

Thr Thr Asn Ser Ser Trp Gly Glu Ile Lys Glu Gly Glu Ile Lys
125 130 135

Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Val Lys
140 145 150

Lys Glu Tyr Ala Leu Phe Tyr Ser Leu Asp Val Val Pro Ile Glu
155 160 165

Asn Asp Asn Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val
170 175 180

Ile Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro Ile
185 190 195

His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys Cys Arg Asp
200 205 210

Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val
215 220 225

Gln Cys Ala His Gly Ile Lys Pro Val Val Ser Thr Gln Leu Leu
230 235 240

Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Ile Ile Arg Ser Ala
245 250 255

Asn Phe Ser Asn Asn Ala Lys Ile Ile Ile Val Gln Leu Arg Glu
260 265 270

```
Pro Val Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
                275                 280                 285

Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr Gly Asp
            290                 295                 300

Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Gly Ala
        305                 310                 315

Lys Trp Asn Asn Thr Leu Lys Lys Val Val Lys Lys Leu Lys Glu
                320                 325                 330

Gln Phe Pro Asn Lys Thr Ile Val Phe Asn His Ser Ser Gly Gly
                335                 340                 345

Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gln Gly Glu Phe
                350                 355                 360

Phe Tyr Cys Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp
        365                 370                 375

Thr Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro Cys
                380                 385                 390

Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Ile Gly Lys Ala
                395                 400                 405

Met Tyr Ala Pro Pro Thr Arg Gly Glu Ile Lys Cys Ser Ser Asn
                410                 415                 420

Ile Thr Gly Leu Leu Leu Ile Arg Asp Gly Gly Ile Asn Thr Ser
                425                 430                 435

Asp Ala Thr Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp
        440                 445                 450

Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
                455                 460                 465

Pro Leu Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
                470                 475                 480

Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu Gly Phe
                485                 490                 495

Leu Gly Ala Xaa Ser Phe
                500 501
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1503 base pairs
- (B) TYPE: Nucleic Acid
- (C) STRANDEDNESS: Single
- (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
GGG GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA 36
Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
  1               5                  10

TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
        15                  20                  25
```

```
CAT AAT GTT TGG GCC ACA CAT GCT TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
                30                  35

CCA AAC CCA CAA GAA ATG GTA TTG GAA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Met Val Leu Glu Asn Val Thr Glu
     40                  45                  50

GAT TTT AAC ATG TGG AAA AAT GAC ATG GTA GAA CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Asp Met Val Glu Gln Met
            55                  60

CAT GAG ANT ATA ATC AGT TTA TGG GAT CAA AGC CTA AAA 231
His Glu Xaa Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys
 65                  70                  75

CCA TGT GTA AAA TTA ACC CCA CTC TGT ATT ACT TTA AAT 270
Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
          80                  85                  90

TGC ACC AAT TGG AAG GAG AAT GAT ACT AAA ACT AAT AGT 309
Cys Thr Asn Trp Lys Glu Asn Asp Thr Lys Thr Asn Ser
                95                  100

AGT AGT ACT ACA ACT AAT AAT AGT AGT GCT ACA GCT AAT 348
Ser Ser Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn
    105                 110                 115

AGT AGT AGT ACT ACA ACT AAT AGT AGT TGG GGA GAG ATA 387
Ser Ser Ser Thr Thr Thr Asn Ser Ser Trp Gly Glu Ile
            120                 125

AAG GAG GGA GAA ATA AAG AAC TGC TCT TTC AAT ATC ACC 426
Lys Glu Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr
130                 135                 140

ACA GGC ATA AGA GAC AAG GTG AAG AAA GAA TAT GCA CTT 465
Thr Gly Ile Arg Asp Lys Val Lys Lys Glu Tyr Ala Leu
        145                 150                 155

TTT TAT AGC CTT GAT GTA GTA CCA ATA GAA AAT GAT AAT 504
Phe Tyr Ser Leu Asp Val Val Pro Ile Glu Asn Asp Asn
                160                 165

ACT AGC TAT AGG TTG AGA AGT TGT AAC ACC TCA GTC ATT 543
Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val Ile
    170                 175                 180

ACA CAA GCC TGT CCA AAG GTA ACT TTT GAG CCA ATT CCC 582
Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro
            185                 190

ATA CAT TAT TGT ACC CCG GCT GGT TTT GCG ATT CTG AAG 621
Ile His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys
195                 200                 205

TGT AAA GAT AAA AAG TTC AAT GGA ACA GGA CCA TGC AAA 660
Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys
        210                 215                 220

AAT GTT AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG CCA 699
Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys Pro
                225                 230
```

```
GTA GTG TCA ACT CAA CTG CTG TTA AAT GGC AGC CTA GCA 738
Val Val Ser Thr Gln Leu Leu L u Asn Gly Ser Leu Ala
    235                 240                 245

GAA GAA GAG GTA ATA ATT AGA TCT GCC AAT TTC TCA AAC 777
Glu Glu Glu Val Ile Ile Arg Ser Ala Asn Phe Ser Asn
            250                 255

AAT GCT AAA ATC ATA ATA GTA CAG TTG AAG GAA CCT GTA 816
Asn Ala Lys Ile Ile Ile Val Gln Leu Lys Glu Pro Val
260                 265                 270

GAA ATT AAT TGT ACA AGA CCC AGC AAC AAT ACA ATA AAA 855
Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
        275                 280                 285

GGT ATA CAC ATA GGA CCA GGG AGA GCA TTT TAT GCA ACA 894
Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr
                290                 295

GGA GAC ATA CGA GGA GAT ATA AGA CAA GCA CAT TGT AAC 933
Gly Asp Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn
    300                 305                 310

ATT AGT GGA GCA AAA TGG AAT AAC ACT TTA AAG AAG GTA 972
Ile Ser Gly Ala Lys Trp Asn Asn Thr Leu Lys Lys Val
            315                 320

GTT ATA AAA TTA AAA GAA CAA TTT CCA AAT AAA ACA ATA 1011
Val Ile Lys Leu Lys Glu Gln Phe Pro Asn Lys Thr Ile
325                 330                 335

GTC TTT AAC CAT TCC TCA GGA GGG GAC CCA GAA ATT GTA 1050
Val Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val
        340                 345                 350

ATG CAC AGT TTT AAT TGT CAA GGG GAA TTT TTC TAC TGT 1089
Met His Ser Phe Asn Cys Gln Gly Glu Phe Phe Tyr Cys
                355                 360

AAT ACA ACG AAG CTG TTT AAT AGT ACT TGG AAT GAT ACT 1128
Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp Thr
    365                 370                 375

ACA GAG TCA AAT AAC AAT GAT AGT ACT ATT ACA CTC CCA 1167
Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro
            380                 385

TGC AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA 1206
Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val
390                 395                 400

GGA AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA GAA ATT 1245
Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile
        405                 410                 415

AAA TGT TCA TCA AAT ATT ACA GGA CTA CTG TTA ACA AGA 1284
Lys Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg
                420                 425

GAT GGT GGT ATT AAC ACT AGC GAT GCC ACC GAG ACC TTC 1323
Asp Gly Gly Ile Asn Thr Ser Asp Ala Thr Glu Thr Phe
    430                 435                 440
```

```
AGA CCG GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT 1362
Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser
              445                 450

GAA TTA TAT AAA TAT AAA GTA GTG AAA ATT GAG CCA TTA 1401
Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
455                 460                 465

GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG 1440
Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
        470                 475                 480

AGA GAA AAA AGA GCA GTA ACA CTA GGA GCT ATG TTC CTT 1479
Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu
                485                 490

GGG TTC TTG GGA GCA TAA AGC TTC 1503
Gly Phe Leu Gly Ala Xaa Ser Phe
    495                 500 501
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 501 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala
 1               5                  10                  15

Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala
            20                  25                  30

Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Met Val
        35                  40                  45

Leu Glu Asn Val Thr Glu Asp Phe Asn Met Trp Lys Asn Asp Met
    50                  55                  60

Val Glu Gln Met His Glu Xaa Ile Ile Ser Leu Trp Asp Gln Ser
65                  70                  75

Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Ile Thr Leu Asn
            80                  85                  90

Cys Thr Asn Trp Lys Glu Asn Asp Thr Lys Thr Asn Ser Ser Ser
        95                  100                 105

Thr Thr Thr Asn Asn Ser Ser Ala Thr Ala Asn Ser Ser Ser Thr
    110                 115                 120

Thr Thr Asn Ser Ser Trp Gly Glu Ile Lys Glu Gly Glu Ile Lys
125                 130                 135

Asn Cys Ser Phe Asn Ile Thr Thr Gly Ile Arg Asp Lys Val Lys
            140                 145                 150

Lys Glu Tyr Ala Leu Phe Tyr Ser Leu Asp Val Val Pro Ile Glu
        155                 160                 165

Asn Asp Asn Thr Ser Tyr Arg Leu Arg Ser Cys Asn Thr Ser Val
    170                 175                 180

Ile Thr Gln Ala Cys Pro Lys Val Thr Phe Glu Pro Ile Pro Ile
185                 190                 195
```

His Tyr Cys Thr Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp
200 205 210

Lys Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val
215 220 225

Gln Cys Thr His Gly Ile Lys Pro Val Val Ser Thr Gln Leu Leu
230 235 240

Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Ile Ile Arg Ser Ala
245 250 255

Asn Phe Ser Asn Asn Ala Lys Ile Ile Ile Val Gln Leu Lys Glu
260 265 270

Pro Val Glu Ile Asn Cys Thr Arg Pro Ser Asn Asn Thr Ile Lys
275 280 285

Gly Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr Gly Asp
290 295 300

Ile Arg Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Gly Ala
305 310 315

Lys Trp Asn Asn Thr Leu Lys Lys Val Val Ile Lys Leu Lys Glu
320 325 330

Gln Phe Pro Asn Lys Thr Ile Val Phe Asn His Ser Ser Gly Gly
335 340 345

Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gln Gly Glu Phe
350 355 360

Phe Tyr Cys Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Asp
365 370 375

Thr Thr Glu Ser Asn Asn Asn Asp Ser Thr Ile Thr Leu Pro Cys
380 385 390

Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala
395 400 405

Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile Lys Cys Ser Ser Asn
410 415 420

Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ile Asn Thr Ser
425 430 435

Asp Ala Thr Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp
440 445 450

Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
455 460 465

Pro Leu Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln
470 475 480

Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu Gly Phe
485 490 495

Leu Gly Ala Xaa Ser Phe
500 501

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1461 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
G   GTA CCT GTA TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
    Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
      1               5                  10

TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His
         15                  20                  25

AAT GTT TGG GCT ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                30                  35

AAC CCA CAA GAA GTA GTA TTG GAA AAT GTA ACA GAA AAT 154
Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn
     40                  45                  50

TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
            55                  60

GAG GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA AAG CCA 232
Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
 65                  70                  75

TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
         80                  85                  90

ACT AAT TTG GAG AAT GCT AAT AAT ACC GAG AAT GCT AAT 310
Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn
                95                 100

AAT ACC AAT AAT TAT ACC TTG GGG ATG GAG AGA GGT GAA 349
Asn Thr Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu
    105                 110                 115

ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC TTA AGA 388
Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Leu Arg
            120                 125

GAT AAG GTG AAA AAA GAA TAT GCA TTG TTT TAT AAA CTT 427
Asp Lys Val Lys Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
130                 135                 140

GAT GTA GTA CAA ATA GAT AAT AGT ACC AAC TAT AGG CTG 466
Asp Val Val Gln Ile Asp Asn Ser Thr Asn Tyr Arg Leu
        145                 150                 155

ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
                160                 165

AAG GTA TCC TTT GAG CTA ATT CCC ATA CAT TAT TGT GCC 544
Lys Val Ser Phe Glu Leu Ile Pro Ile His Tyr Cys Ala
    170                 175                 180

CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG AAG 583
Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys
            185                 190
```

```
TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGC ACA GTA 622
Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val
195                 200                 205

CAA TGT ACA CAT GGA ATT AGA CCA GTA GTA TCA ACT CAA 661
Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
        210                 215                 220

CTA CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG ATA GTA 700
Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Ile Val
                225                 230

ATT AGA TCT GAA AAT ATC ACA GAC AAT GCT AAA ACC ATA 739
Ile Arg Ser Glu Asn Ile Thr Asp Asn Ala Lys Thr Ile
    235                 240                 245

ATA GTG CAG CTA AAT GAA TCT ATA GTG ATT AAT TGT ACA 778
Ile Val Gln Leu Asn Glu Ser Ile Val Ile Asn Cys Thr
            250                 255

AGA CCC AAT AAC AAC ACA AGA AAA AGT ATA AAT ATA GGA 817
Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn Ile Gly
260                 265                 270

CCA GGG AGA GCA TTC TAT ACA ACA GGA GAC ATA ATA GGA 856
Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
        275                 280                 285

GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AAA ACA CAA 895
Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln
                290                 295

TGG GAA AAA ACG TTA AGA CAG ATA GCT ATA AAA TTA GAA 934
Trp Glu Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu
    300                 305                 310

GAA AAA TTT AAG AAT AAA ACA ATA GCC TTT AAT AAA TCC 973
Glu Lys Phe Lys Asn Lys Thr Ile Ala Phe Asn Lys Ser
            315                 320

TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT 1012
Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn
325                 330                 335

TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA AAA CTG 1051
Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Lys Leu
        340                 345                 350

TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn
                355                 360

ACC GGG AAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
Thr Gly Asn Arg Thr Glu Glu Leu Asn Ile Thr Leu Pro
    365                 370                 375

TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val
            380                 385

GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile
390                 395                 400
```

```
AGA TGT TCA TCA AAT ATT ACA GGG CTA CTA TTA ACA AGA 1246
Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg
        405                 410                 415

GAT GGT GGA AGT AAC ACC GGT GAC AAC AGG ACT GAG ACC 1285
Asp Gly Gly Ser Asn Thr Gly Asp Asn Arg Thr Glu Thr
                420                 425

TTT AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG AGA 1324
Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg
    430                 435                 440

AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro
            445                 450

TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTG GTG 1402
Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val
455                 460                 465

CAA AGA GAA AAA AGA GCA GTG GGG ATA GGA GCT ATG TTC 1441
Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
        470                 475                 480

CTT GGG TTC TTG GGA GAT AA 1461
Leu Gly Phe Leu Gly Asp
                485 486
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 486 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala Ser
  1               5                  10                  15

Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala Thr
             20                  25                  30

His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val Val Leu
         35                  40                  45

Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val
     50                  55                  60

Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65                  70                  75

Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
             80                  85                  90

Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn Asn Thr
         95                 100                 105

Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu Ile Lys Asn Cys
    110                 115                 120

Ser Phe Asn Ile Thr Thr Ser Leu Arg Asp Lys Val Lys Lys Glu
125                 130                 135

Tyr Ala Leu Phe Tyr Lys Leu Asp Val Val Gln Ile Asp Asn Ser
    140                 145                 150
```

```
Thr Asn Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln
155                 160                 165

Ala Cys Pro Lys Val Ser Phe Glu Leu Ile Pro Ile His Tyr Cys
170                 175                 180

Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys Phe
185                 190                 195

Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val Gln Cys Thr
200                 205                 210

His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly
215                 220                 225

Ser Leu Ala Glu Glu Glu Ile Val Ile Arg Ser Glu Asn Ile Thr
230                 235                 240

Asp Asn Ala Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Ile Val
245                 250                 255

Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn
260                 265                 270

Ile Gly Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
275                 280                 285

Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln Trp Glu
290                 295                 300

Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu Glu Lys Phe Lys
305                 310                 315

Asn Lys Thr Ile Ala Phe Asn Lys Ser Ser Gly Gly Asp Pro Glu
320                 325                 330

Ile Val Met His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys
335                 340                 345

Asn Thr Thr Lys Leu Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro
350                 355                 360

Phe Ser Asn Thr Gly Asn Arg Thr Glu Glu Leu Asn Ile Thr Leu
365                 370                 375

Pro Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val Gly
380                 385                 390

Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile Arg Cys Ser
395                 400                 405

Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser Asn
410                 415                 420

Thr Gly Asp Asn Arg Thr Glu Thr Phe Arg Pro Gly Gly Gly Asp
425                 430                 435

Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val
440                 445                 450

Arg Ile Glu Pro Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg
455                 460                 465

Val Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
470                 475                 480
```

```
Leu Gly Phe Leu Gly Asp
                485 486

(2) INFORMATION FOR SEQ ID NO:7:
  (i) SEQUENCE CHARACTERISTICS:
      (A) LENGTH: 1474 base pairs
      (B) TYPE: Nucleic Acid
      (C) STRANDEDNESS: Single
      (D) TOPOLOGY: Linear
  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

G   GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT CTA TTT 37
    Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
      1               5                  10

TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His
          15                  20                  25

AAT GTT TGG GCT ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                30                  35

AAC CCA CAA GAA GTA GTA TTG GAA AAT GTA ACA GAA AAT 154
Asn Pro Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn
     40                  45                  50

TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
          55                  60

GAG GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA AAG CCA 232
Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
 65                  70                  75

TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
          80                  85                  90

ACT AAT TTG GAG AAT GCT AAT AAT ACC GAG AAT GCT AAT 310
Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn
                95                  100

AAT ACC AAT AAT TAT ACC TTG GGG ATG GAG AGA GGT GAA 349
Asn Thr Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu
     105                 110                 115

AGA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC TTA AGA 388
Arg Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Leu Arg
          120                 125

GAT AAG GGG AAA AAA GAA TAT GCA TTG TTT TAT AAA CTT 427
Asp Lys Gly Lys Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
130                 135                 140

GAT GTA GTA CAA ATA GAT AAT AGT ACC AAC TAT AGG CTG 466
Asp Val Val Gln Ile Asp Asn Ser Thr Asn Tyr Arg Leu
          145                 150                 155

ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
                160                 165
```

```
AAG GTA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT GCC 544
Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
    170                 175                 180

CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG AAG 583
Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys
            185                 190

TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGG ACA GTA 622
Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Arg Thr Val
195                 200                 205

CAA TGT ACA CAT GGA ATT AGA CCA GTA GTA TCA ACT CAA 661
Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
        210                 215                 220

CTA CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG ATA GTA 700
Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Ile Val
                225                 230

ATT AGA TCT GAA AAT ATC ACA GAC AAT GCT AAA ACC ATA 739
Ile Arg Ser Glu Asn Ile Thr Asp Asn Ala Lys Thr Ile
    235                 240                 245

ATA GTG CAG CTA AAT GAA TCT ATA GTG ATT AAT TGT ACA 778
Ile Val Gln Leu Asn Glu Ser Ile Val Ile Asn Cys Thr
            250                 255

AGA CCC AAT AAC AAC ACA AGA AAA AGT ATA AAT ATA GGA 817
Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn Ile Gly
260                 265                 270

CCA GGG AGA GCA TTC TAT ACA ACA GGA GAC ATA ATA GGA 856
Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
        275                 280                 285

GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AAA ACA CAA 895
Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln
                290                 295

TGG GAA AAA ACG TTA AGA CAG ATA GCT ATA AAA TTA GAA 934
Trp Glu Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu
    300                 305                 310

GAA AAA TTT AAG AAT AAA ACA ATA GCC TTT AAT AAA TCC 973
Glu Lys Phe Lys Asn Lys Thr Ile Ala Phe Asn Lys Ser
            315                 320

TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT 1012
Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn
325                 330                 335

TGT GGA GGG GGA TTT TTC TAC TGT AGT ACG AGA AAA CTG 1051
Cys Gly Gly Gly Phe Phe Tyr Cys Ser Thr Arg Lys Leu
        340                 345                 350

TTT AAT AGT ACC TGG AAT TTA ACA CAA CCG TTT AGT AAT 1090
Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro Phe Ser Asn
                355                 360

ACC GGG GAT CGT ACT GAA GAG TTA AAT ATT ACA CTC CCA 1129
Thr Gly Asp Arg Thr Glu Glu Leu Asn Ile Thr Leu Pro
    365                 370                 375
```

```
TGC AGA ATA AAA CAA ATC ATA AAC TTG TGG CAG GAA GTA 1168
Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val
            380                 385

GGC AAA GCA ATG TAT GCC CCT CCC ATC AGA GGA CAA ATT 1207
Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile
390                 395                 400

AGA TGT TCA TCA AAT ATT ACA GGG CTA CTA TTA AGG AGA 1246
Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Arg Arg
        405                 410                 415

GAT GGT GGA AGT AAC ACC AGT GAC AAC CAG ACT GAG ACC 1285
Asp Gly Gly Ser Asn Thr Ser Asp Asn Gln Thr Glu Thr
                420                 425

TTT AGA CCT GGG GGA GGA GAT ATG AGG GAC AAG TGG AGA 1324
Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Lys Trp Arg
    430                 435                 440

AGT GAA TTA TAT AAA TAT AAA GTA GTA AGA ATT GAA CCA 1363
Ser Glu Leu Tyr Lys Tyr Lys Val Val Arg Ile Glu Pro
            445                 450

TTA GGA GTA GCA CCC ACC CAG GCA AAG AGA AGA GTG GTG 1402
Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg Val Val
455                 460                 465

CAA AGA GAA AAA AGA GCA GTG GGG ATA GGA GCT ATG TTC 1441
Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
        470                 475                 480

CTT AGG TTC TTA GGA GAT AAA GCT TCT AGA GTC 1474
Leu Arg Phe Leu Gly Asp Lys Ala Ser Arg Val
                485                 490 491
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 491 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala Ser
 1               5                  10                  15

Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala Thr
            20                  25                  30

His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val Val Leu
        35                  40                  45

Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val
    50                  55                  60

Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
65                  70                  75

Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
            80                  85                  90

Thr Asn Leu Glu Asn Ala Asn Asn Thr Glu Asn Ala Asn Asn Thr
        95                  100                 105
```

Asn Asn Tyr Thr Leu Gly Met Glu Arg Gly Glu Arg Lys Asn Cys
110 115 120

Ser Phe Asn Ile Thr Thr Ser Leu Arg Asp Lys Gly Lys Lys Glu
125 130 135

Tyr Ala Leu Phe Tyr Lys Leu Asp Val Val Gln Ile Asp Asn Ser
140 145 150

Thr Asn Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln
155 160 165

Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
170 175 180

Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys Phe
185 190 195

Asn Gly Thr Gly Pro Cys Lys Asn Val Arg Thr Val Gln Cys Thr
200 205 210

His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly
215 220 225

Ser Leu Ala Glu Glu Glu Ile Val Ile Arg Ser Glu Asn Ile Thr
230 235 240

Asp Asn Ala Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Ile Val
245 250 255

Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Asn
260 265 270

Ile Gly Pro Gly Arg Ala Phe Tyr Thr Thr Gly Asp Ile Ile Gly
275 280 285

Asp Ile Arg Gln Ala His Cys Asn Leu Ser Lys Thr Gln Trp Glu
290 295 300

Lys Thr Leu Arg Gln Ile Ala Ile Lys Leu Glu Glu Lys Phe Lys
305 310 315

Asn Lys Thr Ile Ala Phe Asn Lys Ser Ser Gly Gly Asp Pro Glu
320 325 330

Ile Val Met His Ser Phe Asn Cys Gly Gly Gly Phe Phe Tyr Cys
335 340 345

Ser Thr Arg Lys Leu Phe Asn Ser Thr Trp Asn Leu Thr Gln Pro
350 355 360

Phe Ser Asn Thr Gly Asp Arg Thr Glu Glu Leu Asn Ile Thr Leu
365 370 375

Pro Cys Arg Ile Lys Gln Ile Ile Asn Leu Trp Gln Glu Val Gly
380 385 390

Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile Arg Cys Ser
395 400 405

Ser Asn Ile Thr Gly Leu Leu Leu Arg Arg Asp Gly Gly Ser Asn
410 415 420

Thr Ser Asp Asn Gln Thr Glu Thr Phe Arg Pro Gly Gly Gly Asp
425 430 435

```
Met Arg Asp Lys Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val
                440                 445                 450

Arg Ile Glu Pro Leu Gly Val Ala Pro Thr Gln Ala Lys Arg Arg
                455                 460                 465

Val Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Met Phe
                470                 475                 480

Leu Arg Phe Leu Gly Asp Lys Ala Ser Arg Val
                485                 490 491
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1512 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
CTC GAG GTA CCT GTA TGG AAA GAA GCA ACT ACC ACT 36
Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
  1               5                  10

CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
        15                  20                  25

AAA CAT AAT GTT TGG GCC ACA CAC GCC TGT GTA CCC ACA 114
Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
                30                  35

GAT CCC AAC CCA CAA GAA GTA GTA TTG GGA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Val Leu Gly Asn Val Thr
     40                  45                  50

GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
            55                  60

ATG CAT GAA GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA 231
Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65                  70                  75

AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA 270
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
        80                  85                  90

AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn
                95                  100

AGT AGT GCC ACT ACC AAT AGT AGT AGT TGG GAA GAA ATG 348
Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met
    105                 110                 115

AAG GGG GAA ATG AAA AGA TGC TCT TTC AAT ATC ACC ACA 387
Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr
            120                 125

AGC ATA AGA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe
130                 135                 140
```

```
TAT AGA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACC 465
Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr
        145                 150                 155

ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr
                160                 165

CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile
    170                 175                 180

CAT TTT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys
            185                 190

AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn
195                 200                 205

GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660
Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val
        210                 215                 220

GTG TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA 699
Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
                225                 230

GAA GAG GTA ATA ATT AGA TCT GAC AAT ATC ACA GAC AAT 738
Glu Glu Val Ile Ile Arg Ser Asp Asn Ile Thr Asp Asn
    235                 240                 245

ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
Thr Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Val
            250                 255

ATT AAT TGT ACA AGA CCC AAC AAC AAT ACA AGA AAA AGT 816
Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Ser
260                 265                 270

ATA CAT ATA GGA CCA GGG AGT GCA TTT TTT GCA ACA GGA 855
Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
        275                 280                 285

GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894
Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu
                290                 295

AGT AGA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val
    300                 305                 310

ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu
            315                 320

AAA ACA ATA GTC TTT AAT CGA TCC TCA GGA GGG GAC CCG 1011
Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro
325                 330                 335

GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe
        340                 345                 350
```

```
TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
                355                 360

AAT GTT ACT AAA GGG TTG AAT AAC ACT GAA GGA AAT AGC 1128
Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
    365                 370                 375

ACA GGA GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys
            380                 385

CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
390                 395                 400

TAT GCC CCT CCC ATC AGT GGA CAA ATT AGA TGT TCA TCA 1245
Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser
        405                 410                 415

AAC ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT AGT 1284
Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser
                420                 425

AAG AAC GAG AGC ATC ACC ACC GAG GTC TTC AGA CCT GGA 1323
Lys Asn Glu Ser Ile Thr Thr Glu Val Phe Arg Pro Gly
    430                 435                 440

GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT GAA TTA TAT 1362
Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
            445                 450

AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCG 1401
Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
455                 460                 465

CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA 1440
Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
        470                 475                 480

AGA GCA GTG GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
                485                 490

TTG GGA GCA TAA AGC TTC TAG AGT CGA CCT GCA 1512
Leu Gly Ala Xaa Ser Phe Xaa Ser Arg Pro Ala
    495                 500                 504
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 504 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys
  1               5                  10                  15

Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu Lys His Asn Val Trp
                20                  25                  30

Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val
                35                  40                  45
```

Val Leu Gly Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn
50 55 60

Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln
65 70 75

Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
80 85 90

Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn Ser Ser
95 100 105

Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met Lys Gly Glu Met
110 115 120

Lys Arg Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Ile
125 130 135

Lys Lys Glu His Ala Leu Phe Tyr Arg Leu Asp Val Val Pro Ile
140 145 150

Asp Asn Asp Asn Thr Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser
155 160 165

Val Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro
170 175 180

Ile His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn
185 190 195

Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn Val Ser Thr
200 205 210

Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln Leu
215 220 225

Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Ile Ile Arg Ser
230 235 240

Asp Asn Ile Thr Asp Asn Thr Lys Thr Ile Ile Val Gln Leu Asn
245 250 255

Glu Ser Val Val Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg
260 265 270

Lys Ser Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
275 280 285

Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu Ser Arg
290 295 300

Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val Ile Lys Leu Arg
305 310 315

Glu Gln Phe Arg Lys Gln Phe Gly Glu Lys Thr Ile Val Phe Asn
320 325 330

Arg Ser Ser Gly Gly Asp Pro Glu Ile Ala Met His Ser Phe Asn
335 340 345

Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn
350 355 360

Ser Thr Trp Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn
365 370 375

```
Ser Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys Gln
                380                 385                 390

Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro
            395                 400                 405

Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu
            410                 415                 420

Leu Leu Thr Arg Asp Gly Gly Ser Lys Asn Glu Ser Ile Thr Thr
            425                 430                 435

Glu Val Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg
            440                 445                 450

Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly
            455                 460                 465

Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
            470                 475                 480

Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe Leu Gly
            485                 490                 495

Ala Xaa Ser Phe Xaa Ser Arg Pro Ala
            500             504
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1501 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
   CTC GAG GTA CCT GTG TGG AAA GAA GCA ACT ACC ACT 36
   Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
     1               5                  10

CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT AAT ACA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu
         15                  20                  25

AAA CAT AAT GTT TGG GCC ACA CAC GCC TGT GTA CCC ACA 114
Lys His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
                 30                  35

GAT CCC AAC CCA CAA GAA GTA GTA TTG GGA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Val Leu Gly Asn Val Thr
     40                  45                  50

GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
             55                  60

ATG CAT GAA GAT ATA ATC AGT TTA TGG GAT CAA AGT CTA 231
Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65                  70                  75

AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA 270
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
         80                  85                  90
```

```
AAT TGC ACT GAT GAT TTA GGG AAT GCT ACT AAT ACC AAT 309
Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn
                 95                  100

AGC AGT GCC ACT ACC AAT AGT AGT AGT TGG GAA GAA ATG 348
Ser Ser Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met
    105                 110                 115

AAG GGG GAA ATG AAA AGG TGC TCT TTC AAT ATC ACC ACA 387
Lys Gly Glu Met Lys Arg Cys Ser Phe Asn Ile Thr Thr
            120                 125

AGC ATA AGA GAT AAG ATT AAG AAA GAA CAT GCA CTT TTC 426
Ser Ile Arg Asp Lys Ile Lys Lys Glu His Ala Leu Phe
130                 135                 140

TAT AGA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACC 465
Tyr Arg Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr
        145                 150                 155

ACA TAT AGG TTG ATA AAT TGT AAT ACC TCA GTC ATT ACA 504
Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser Val Ile Thr
            160                 165

CAG GCC TGT CCA AAG GTA TCA TTT GAG CCA ATT CCC ATA 543
Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile
    170                 175                 180

CAT TTT TGT GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT 582
His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys
            185                 190

AAT AAT AAG ACG TTC GAG GGA AAA GGA CCA TGT AAA AAT 621
Asn Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn
195                 200                 205

GTC AGT ACA GTA CAA TGC ACA CAT GGA ATT AGG CCA GTA 660
Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val
        210                 215                 220

GTG TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA 699
Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
            225                 230

GAA GAG GTA ATA ATT AGA TCT GGC AAT ATC ACA GAC AAT 738
Glu Glu Val Ile Ile Arg Ser Gly Asn Ile Thr Asp Asn
    235                 240                 245

ACT AAA ACC ATT ATA GTA CAG CTA AAC GAA TCT GTA GTA 777
Thr Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Val
            250                 255

ATT AAT TGT ACA AGA TCC AAC AAC AAT ACA AGA AAA AGT 816
Ile Asn Cys Thr Arg Ser Asn Asn Asn Thr Arg Lys Ser
260                 265                 270

ATA CAT ATA GGA CCA GGG AGT GCA TTT TTT GCA ACA GGA 855
Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
        275                 280                 285

GAA ATA ATA GGA GAT ATA AGA CAA GCA CAC TGT AAC CTT 894
Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu
            290                 295
```

```
AGT AGA ACA CAA TGG AAT AAC ACT TTA GGA AAG ATA GTC 933
Ser Arg Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val
    300                 305                 310

ATA AAA TTA AGA GAA CAA TTT AGA AAA CAA TTT GGA GAA 972
Ile Lys Leu Arg Glu Gln Phe Arg Lys Gln Phe Gly Glu
            315                 320

AAA ACA ATA GTC TTT AAT CGA TCC TCA GGA GGG GAC CCG 1011
Lys Thr Ile Val Phe Asn Arg Ser Ser Gly Gly Asp Pro
325                 330                 335

GAA ATT GCA ATG CAC AGT TTT AAT TGT GGA GGG GAA TTT 1050
Glu Ile Ala Met His Ser Phe Asn Cys Gly Gly Glu Phe
        340                 345                 350

TTC TAC TGT AAC ACA ACA GCA CTG TTT AAT AGT ACC TGG 1089
Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn Ser Thr Trp
                355                 360

AAT GTT ACT AAA GGG TTG AAT AAC ACT GAA GGA AAT AGC 1128
Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn Ser
    365                 370                 375

ACA GGG GAT GAA AAT ATC ATA CTC CCA TGT AGA ATA AAA 1167
Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys
            380                 385

CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA ATG 1206
Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
390                 395                 400

TAT GCC CCT CCC ATC AGT GGA CAA ATT AGA TGT TCA TCA 1245
Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser
        405                 410                 415

AAT ATT ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT AGT 1284
Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Ser
                420                 425

AAG AAC GAG AGC ATC ACC ACC GAG GTC TTC AGA CCT GGA 1323
Lys Asn Glu Ser Ile Thr Thr Glu Val Phe Arg Pro Gly
    430                 435                 440

GGA GGA GAT ATG AGG GAC AAT TGG AGA AGT GAA TTA TAT 1362
Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr
            445                 450

AAA TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCG 1401
Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
455                 460                 465

CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA 1440
Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
        470                 475                 480

AGA GCA GTG GGA ACA ATA GGA GCT ATG TTC CTT GGG TTC 1479
Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe
                485                 490

TTA GGA GCA TAA AGC TTC TAG A 1501
Leu Gly Ala Xaa Ser Phe Xaa
    495                 500
```

(2) INFORMATION FOR SEQ ID NO:12:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 500 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys
1 5 10 15

Ala Ser Asp Ala Lys Ala Tyr Asn Thr Glu Lys His Asn Val Trp
20 25 30

Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val
35 40 45

Val Leu Gly Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn
50 55 60

Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln
65 70 75

Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
80 85 90

Asn Cys Thr Asp Asp Leu Gly Asn Ala Thr Asn Thr Asn Ser Ser
95 100 105

Ala Thr Thr Asn Ser Ser Ser Trp Glu Glu Met Lys Gly Glu Met
110 115 120

Lys Arg Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Ile
125 130 135

Lys Lys Glu His Ala Leu Phe Tyr Arg Leu Asp Val Val Pro Ile
140 145 150

Asp Asn Asp Asn Thr Thr Tyr Arg Leu Ile Asn Cys Asn Thr Ser
155 160 165

Val Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro
170 175 180

Ile His Phe Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn
185 190 195

Asn Lys Thr Phe Glu Gly Lys Gly Pro Cys Lys Asn Val Ser Thr
200 205 210

Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln Leu
215 220 225

Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Ile Ile Arg Ser
230 235 240

Gly Asn Ile Thr Asp Asn Thr Lys Thr Ile Ile Val Gln Leu Asn
245 250 255

Glu Ser Val Val Ile Asn Cys Thr Arg Ser Asn Asn Asn Thr Arg
260 265 270

Lys Ser Ile His Ile Gly Pro Gly Ser Ala Phe Phe Ala Thr Gly
275 280 285

```
Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu Ser Arg
                290                 295                 300

Thr Gln Trp Asn Asn Thr Leu Gly Lys Ile Val Ile Lys Leu Arg
305                 310                 315

Glu Gln Phe Arg Lys Gln Phe Gly Glu Lys Thr Ile Val Phe Asn
                320                 325                 330

Arg Ser Ser Gly Gly Asp Pro Glu Ile Ala Met His Ser Phe Asn
                335                 340                 345

Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Ala Leu Phe Asn
                350                 355                 360

Ser Thr Trp Asn Val Thr Lys Gly Leu Asn Asn Thr Glu Gly Asn
                365                 370                 375

Ser Thr Gly Asp Glu Asn Ile Ile Leu Pro Cys Arg Ile Lys Gln
                380                 385                 390

Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro
                395                 400                 405

Pro Ile Ser Gly Gln Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu
                410                 415                 420

Leu Leu Thr Arg Asp Gly Gly Ser Lys Asn Glu Ser Ile Thr Thr
                425                 430                 435

Glu Val Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg
                440                 445                 450

Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly
                455                 460                 465

Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
                470                 475                 480

Arg Ala Val Gly Thr Ile Gly Ala Met Phe Leu Gly Phe Leu Gly
                485                 490                 495

Ala Xaa Ser Phe Xaa
                500
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1514 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
GG  GAA TTC GGA TCC GGG GTA CCT GTG TGG AAG GAA GCA 38
    Glu Phe Gly Ser Gly Val Pro Val Trp Lys Glu Ala
      1               5                  10

ACC ACC ACT CTA TTC TGT GCA TCA GAT GCT AGA GCA TAT 77
Thr Thr Thr Leu Phe Cys Ala Ser Asp Ala Arg Ala Tyr
        15                  20                  25

GAC ACA GAG GTA CAT AAT GTT TGG GCC ACA CAT GCC TGT 116
Asp Thr Glu Val His Asn Val Trp Ala Thr His Ala Cys
                30                  35
```

```
GTA CCC ACA GAC CCT AGT CCA CAA GAA GTA GTT TTG GAA 155
Val Pro Thr Asp Pro Ser Pro Gln Glu Val Val Leu Glu
     40                  45                  50

AAT GTG ACA GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG 194
Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met
          55                  60

GTA GAA CAA ATG CAT GAG GAT ATA ATT AGT TTA TGG GAT 233
Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp
 65                  70                  75

CAA AGC TTA AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT 272
Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys
          80                  85                  90

GTT ACT TTA AAT TGC AGT GAT TAT AGG AAT GCT ACT GAT 311
Val Thr Leu Asn Cys Ser Asp Tyr Arg Asn Ala Thr Asp
               95                  100

TAT AAG AAT GCT ACT GAT ACC ACT AGT AGT AAC GAG GGA 350
Tyr Lys Asn Ala Thr Asp Thr Thr Ser Ser Asn Glu Gly
     105                 110                 115

AAG ATG GAG AGA GGA GAA ATA AAA AAC TGC TCT TTC AAT 389
Lys Met Glu Arg Gly Glu Ile Lys Asn Cys Ser Phe Asn
          120                 125

ATT ACC ACA AGC ATA AAA AAT AAG ATG CAG AAA GAA TAT 428
Ile Thr Thr Ser Ile Lys Asn Lys Met Gln Lys Glu Tyr
130                 135                 140

GCA CTT TTC TAT AAA CTT GAT ATA GTA CCA ATA GAT AAT 467
Ala Leu Phe Tyr Lys Leu Asp Ile Val Pro Ile Asp Asn
          145                 150                 155

ACA AGC TAT ACA TTG ATA AGT TGT AAC ACC TCA GTC ATT 506
Thr Ser Tyr Thr Leu Ile Ser Cys Asn Thr Ser Val Ile
               160                 165

ACA CAG GCC TGT CCA AAG GTA TCC TTT GAA CCA ACT CCC 545
Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Thr Pro
     170                 175                 180

ATA CAT TAT TGT GCT CCG GCT GGT TTT GCG ATT CTA AAG 584
Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys
          185                 190

TGT AAT GAT AAG AAG TTC AGT GGA AAA GGA GAA TGT AAA 623
Cys Asn Asp Lys Lys Phe Ser Gly Lys Gly Glu Cys Lys
195                 200                 205

AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AGG CCA 662
Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro
          210                 215                 220

GTA GTA TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA 701
Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
               225                 230

GAA GAA GAG GTG GTA ATT AGA TCT GAC AAT TTC ATA GAC 740
Glu Glu Glu Val Val Ile Arg Ser Asp Asn Phe Ile Asp
     235                 240                 245
```

```
AAT ACT AAA ACC ATA ATA GTA CAG CTG AAA GAA TCT GTA 779
Asn Thr Lys Thr Ile Ile Val Gln Leu Lys Glu Ser Val
            250                 255

GAA ATT AAT TGT ATA AGA CCC AAC AAT AAT ACA AGA AAA 818
Glu Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr Arg Lys
260                 265                 270

GGT ATA CAT ATA GGA CCA GGG AGA GCA TGG TAT GCA ACA 857
Gly Ile His Ile Gly Pro Gly Arg Ala Trp Tyr Ala Thr
        275                 280                 285

GGA GAA ATA GTA GGA GAT ATA AGA AAG GCA TAT TGT AAC 896
Gly Glu Ile Val Gly Asp Ile Arg Lys Ala Tyr Cys Asn
            290                 295

ATT AGT AGA ACA AAA TGG AAT AAC ACT TTA ATA CAG ATA 935
Ile Ser Arg Thr Lys Trp Asn Asn Thr Leu Ile Gln Ile
    300                 305                 310

GCT AAC AAA TTA AAA GAA AAA TAT AAT ACA ACA ATA AGC 974
Ala Asn Lys Leu Lys Glu Lys Tyr Asn Thr Thr Ile Ser
            315                 320

TTT AAT CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ACG 1013
Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Thr
325                 330                 335

CAT AGT TTT AAT TGT GGA GGG GAG TTT TTC TAC TGT GAT 1052
His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asp
        340                 345                 350

TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT TTA AAT GGT 1091
Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Leu Asn Gly
            355                 360

ACT TGG AAT TTT ACT GCA GGG TCA AAT GAA ACT GAA GGC 1130
Thr Trp Asn Phe Thr Ala Gly Ser Asn Glu Thr Glu Gly
    365                 370                 375

AAT ATC ACA CTC CCA TGC AGA ATA AAA CAA ATT ATA AAC 1169
Asn Ile Thr Leu Pro Cys Arg Ile Lys Gln Ile Ile Asn
            380                 385

AGG TGG CAG GAA GTA GGG AAA GCA ATG TAT GCC CCT CCC 1208
Arg Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro Pro
390                 395                 400

ATC AGT GGA CAA ATA AAA TGC TCA TCA AAC ATT ACA GGG 1247
Ile Ser Gly Gln Ile Lys Cys Ser Ser Asn Ile Thr Gly
        405                 410                 415

ATG ATA TTA ACA AGG GAT GGT GGT AAC GAG AAC AAT AAT 1286
Met Ile Leu Thr Arg Asp Gly Gly Asn Glu Asn Asn Asn
            420                 425

GAG AGC AGT ACT ACT GAG ACC TTC AGA CCG GGA GGA GGA 1325
Glu Ser Ser Thr Thr Glu Thr Phe Arg Pro Gly Gly Gly
    430                 435                 440

GAT ATG AGG AAC AAT TGG AGA AGT GAA TTA TAT AAA TAT 1364
Asp Met Arg Asn Asn Trp Arg Ser Glu Leu Tyr Lys Tyr
            445                 450
```

```
AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCA CCC ACC 1403
Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr
455                 460                 465

AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA AGA GCA 1442
Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala
        470                 475                 480

GTG GGA GCG CTA GGA GCT ATG TTC CTT GGG TTC TTA GGA 1481
Val Gly Ala Leu Gly Ala Met Phe Leu Gly Phe Leu Gly
                485                 490

GCA TAA AGC TTC TAG ACC GAC TCT AGA GGA TCC 1514
Ala Xaa Ser Phe Xaa Thr Asp Ser Arg Gly Ser
    495                 500             504
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 504 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Glu Phe Gly Ser Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr
 1               5                  10                  15

Leu Phe Cys Ala Ser Asp Ala Arg Ala Tyr Asp Thr Glu Val His
            20                  25                  30

Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Ser Pro
        35                  40                  45

Gln Glu Val Val Leu Glu Asn Val Thr Glu Asn Phe Asn Met Trp
    50                  55                  60

Lys Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu
65                  70                  75

Trp Asp Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys
            80                  85                  90

Val Thr Leu Asn Cys Ser Asp Tyr Arg Asn Ala Thr Asp Tyr Lys
        95                  100                 105

Asn Ala Thr Asp Thr Thr Ser Ser Asn Glu Gly Lys Met Glu Arg
    110                 115                 120

Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Lys
125                 130                 135

Asn Lys Met Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu Asp Ile
            140                 145                 150

Val Pro Ile Asp Asn Thr Ser Tyr Thr Leu Ile Ser Cys Asn Thr
        155                 160                 165

Ser Val Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Thr
    170                 175                 180

Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys
185                 190                 195

Asn Asp Lys Lys Phe Ser Gly Lys Gly Glu Cys Lys Asn Val Ser
            200                 205                 210
```

Thr Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
215 220 225

Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Val Ile Arg
230 235 240

Ser Asp Asn Phe Ile Asp Asn Thr Lys Thr Ile Ile Val Gln Leu
245 250 255

Lys Glu Ser Val Glu Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr
260 265 270

Arg Lys Gly Ile His Ile Gly Pro Gly Arg Ala Trp Tyr Ala Thr
275 280 285

Gly Glu Ile Val Gly Asp Ile Arg Lys Ala Tyr Cys Asn Ile Ser
290 295 300

Arg Thr Lys Trp Asn Asn Thr Leu Ile Gln Ile Ala Asn Lys Leu
305 310 315

Lys Glu Lys Tyr Asn Thr Thr Ile Ser Phe Asn Arg Ser Ser Gly
320 325 330

Gly Asp Pro Glu Ile Val Thr His Ser Phe Asn Cys Gly Gly Glu
335 340 345

Phe Phe Tyr Cys Asp Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn
350 355 360

Leu Asn Gly Thr Trp Asn Phe Thr Ala Gly Ser Asn Glu Thr Glu
365 370 375

Gly Asn Ile Thr Leu Pro Cys Arg Ile Lys Gln Ile Ile Asn Arg
380 385 390

Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro Pro Ile Ser Gly
395 400 405

Gln Ile Lys Cys Ser Ser Asn Ile Thr Gly Met Ile Leu Thr Arg
410 415 420

Asp Gly Gly Asn Glu Asn Asn Asn Glu Ser Ser Thr Thr Glu Thr
425 430 435

Phe Arg Pro Gly Gly Gly Asp Met Arg Asn Asn Trp Arg Ser Glu
440 445 450

Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
455 460 465

Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala
470 475 480

Val Gly Ala Leu Gly Ala Met Phe Leu Gly Phe Leu Gly Ala Xaa
485 490 495

Ser Phe Xaa Thr Asp Ser Arg Gly Ser
500 504

(2) INFORMATION FOR SEQ ID NO:15:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1408 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
G   GTA CCT GTG TGG AAG GAA GCA ACC ACC ACT CTA TTC 37
    Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe
      1               5                  10

TGT GCA TCA GAT GCT AGA GCA TAT GAC ACA GAG GTA CAT 76
Cys Ala Ser Asp Ala Arg Ala Tyr Asp Thr Glu Val His
          15                  20                  25

AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC CCT 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                30                  35

AGT CCA CAA GAA GTA TTT TTG GGA AAT GTG ACA GAA AAT 154
Ser Pro Gln Glu Val Phe Leu Gly Asn Val Thr Glu Asn
     40                  45                  50

TTT AAT ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG TAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met Tyr
           55                  60

GAG GAT ATA ATT AGT TTA TGG GAT CAA AGC TTA AAG CCA 232
Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
 65                  70                  75

TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
          80                  85                  90

AGT GAT TAT AGG AAT GCT ACT GAT TAT AAG AAT GCT ACT 310
Ser Asp Tyr Arg Asn Ala Thr Asp Tyr Lys Asn Ala Thr
                95                 100

GAT ACC ACT AGT AGT AAC GAG GGA AAG ATG GAG AGA GGA 349
Asp Thr Thr Ser Ser Asn Glu Gly Lys Met Glu Arg Gly
    105                 110                 115

GAA ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC ATA 388
Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile
          120                 125

AAA AAT AAG ATG CAG AAA GAA TAT GCA CTT TTC TAT AAA 427
Lys Asn Lys Met Gln Lys Glu Tyr Ala Leu Phe Tyr Lys
130                 135                 140

CTT AAT ATA GTA CCA ATA GAT AAT ACA AGC TAT ACA TTG 466
Leu Asn Ile Val Pro Ile Asp Asn Thr Ser Tyr Thr Leu
      145                 150                 155

ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCC TGT CCA 505
Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro
                160                 165

AAG GTA TCC TTT GAA CCA ATT CCC ATA CAT TAT TGT GCT 544
Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
    170                 175                 180

CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG AAG 583
Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys
          185                 190
```

```
TTC AGT GGA AAA GGA GAA TGT AAA AAT CTC AGC ACA GTA 622
Phe Ser Gly Lys Gly Glu Cys Lys Asn Val Ser Thr Val
195                 200                 205

CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT CAA 661
Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln
        210                 215                 220

CTG CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTG GTA 700
Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Val
                225                 230

ATT AGA TCT GAC AAT TTC ACA GAC AAT ACT AAA ACC ATA 739
Ile Arg Ser Asp Asn Phe Thr Asp Asn Thr Lys Thr Ile
    235                 240                 245

ATA GTA CAG CTG AAA GAA TCT GTA GAA ATT AAT TGT ATA 778
Ile Val Gln Leu Lys Glu Ser Val Glu Ile Asn Cys Ile
            250                 255

AGA CCC AAC AAT AAT ACA AGA AAA GGT ATA CAT ATA GGA 817
Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Ile Gly
260                 265                 270

CCA GGG AGA GCA TGG TAT GCA ACA GGA GAA ATA GTA GGA 856
Pro Gly Arg Ala Trp Tyr Ala Thr Gly Glu Ile Val Gly
        275                 280                 285

GAT ATA AGA CAG GCA TAT TGT AAC ATT AGT AGA ACA AAA 895
Asp Ile Arg Gln Ala Tyr Cys Asn Ile Ser Arg Thr Lys
                290                 295

TGG AAT AAC ACT TTA ATA CAG ATA GCT AAC AAA TTA AAA 934
Trp Asn Asn Thr Leu Ile Gln Ile Ala Asn Lys Leu Lys
    300                 305                 310

GAA AAA TAT AAT ACA ACA ATA AGC TTT AAT CGA TCC TCA 973
Glu Lys Tyr Asn Thr Thr Ile Ser Phe Asn Arg Ser Ser
            315                 320

GGA GGG GAC CCA GAA ATT GTA ACC CAT AGT TTT AAT TGT 1012
Gly Gly Asp Pro Glu Ile Val Thr His Ser Phe Asn Cys
325                 330                 335

GGA GGG GAA TTT TTC TAC TGT AAT TCA ACA CAA CTG TTT 1051
Gly Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Leu Phe
        340                 345                 350

AAT AGT ACT TGG AAT TTA AAT GGT ACT TGG AAT TTT ACT 1090
Asn Ser Thr Trp Asn Leu Asn Gly Thr Trp Asn Phe Thr
                355                 360

GCA GGG TCA AAT GAA ACT GAA GGC AAT ATC ACA CTC CCA 1129
Ala Gly Ser Asn Glu Thr Glu Gly Asn Ile Thr Leu Pro
    365                 370                 375

TGC AGA ATA AAA CAA ATT ATA AAC AGG TGG CAG GAA GTA 1168
Cys Arg Ile Lys Gln Ile Ile Asn Arg Trp Gln Glu Val
            380                 385

GGA AAA GCA ATG TAT GCC CCT CCC ATC AGT GGA CAA ATA 1207
Gly Lys Ala Met Tyr Ala Pro Pro Ile Ser Gly Gln Ile
390                 395                 400
```

```
AGA TGC TCA TCA AAC ATT ACA GGG ATG ATA TTA ACA AGG 1246
Arg Cys Ser Ser Asn Ile Thr Gly Met Ile Leu Thr Arg
        405                 410                 415

GAT GGT GGT AAC GAG AAC AAT AAT GAG AGC AGT ACT ACT 1285
Asp Gly Gly Asn Glu Asn Asn Asn Glu Ser Ser Thr Thr
                420                 425

GAG ACC TTC AGA CCG GGA GGA GGA GAT ATG AGG AAC AAT 1324
Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asn Asn
    430                 435                 440

TGG AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT 1363
Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile
            445                 450

GAG CCA TTA GGA GTA GCA CCC ACC GAC TCT AGA GGA TCC 1402
Glu Pro Leu Gly Val Ala Pro Thr Asp Ser Arg Gly Ser
455                 460                 465

TCT AGA 1408
Ser Arg
    469
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 469 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala Ser
 1               5                  10                  15

Asp Ala Arg Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala Thr
            20                  25                  30

His Ala Cys Val Pro Thr Asp Pro Ser Pro Gln Glu Val Phe Leu
        35                  40                  45

Gly Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val
    50                  55                  60

Glu Gln Met Tyr Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
65                  70                  75

Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys
            80                  85                  90

Ser Asp Tyr Arg Asn Ala Thr Asp Tyr Lys Asn Ala Thr Asp Thr
        95                  100                 105

Thr Ser Ser Asn Glu Gly Lys Met Glu Arg Gly Glu Ile Lys Asn
    110                 115                 120

Cys Ser Phe Asn Ile Thr Thr Ser Ile Lys Asn Lys Met Gln Lys
125                 130                 135

Glu Tyr Ala Leu Phe Tyr Lys Leu Asn Ile Val Pro Ile Asp Asn
            140                 145                 150

Thr Ser Tyr Thr Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln
        155                 160                 165
```

Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
170 175 180

Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys Phe
185 190 195

Ser Gly Lys Gly Glu Cys Lys Asn Val Ser Thr Val Gln Cys Thr
200 205 210

His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly
215 220 225

Ser Leu Ala Glu Glu Glu Val Val Ile Arg Ser Asp Asn Phe Thr
230 235 240

Asp Asn Thr Lys Thr Ile Ile Val Gln Leu Lys Glu Ser Val Glu
245 250 255

Ile Asn Cys Ile Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His
260 265 270

Ile Gly Pro Gly Arg Ala Trp Tyr Ala Thr Gly Glu Ile Val Gly
275 280 285

Asp Ile Arg Gln Ala Tyr Cys Asn Ile Ser Arg Thr Lys Trp Asn
290 295 300

Asn Thr Leu Ile Gln Ile Ala Asn Lys Leu Lys Glu Lys Tyr Asn
305 310 315

Thr Thr Ile Ser Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile
320 325 330

Val Thr His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn
335 340 345

Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Leu Asn Gly Thr Trp
350 355 360

Asn Phe Thr Ala Gly Ser Asn Glu Thr Glu Gly Asn Ile Thr Leu
365 370 375

Pro Cys Arg Ile Lys Gln Ile Ile Asn Arg Trp Gln Glu Val Gly
380 385 390

Lys Ala Met Tyr Ala Pro Pro Ile Ser Gly Gln Ile Arg Cys Ser
395 400 405

Ser Asn Ile Thr Gly Met Ile Leu Thr Arg Asp Gly Gly Asn Glu
410 415 420

Asn Asn Asn Glu Ser Ser Thr Thr Glu Thr Phe Arg Pro Gly Gly
425 430 435

Gly Asp Met Arg Asn Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys
440 445 450

Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr Asp Ser Arg
455 460 465

Gly Ser Ser Arg
469

(2) INFORMATION FOR SEQ ID NO:17:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1499 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
GAG GTA CCT GTG TGG AAA GAA GCA ACC ACT ACT CTA 36
Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
  1               5                  10

TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GGG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Gly Val
        15                  20                  25

CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
                30                  35

CCC AAC CCA CAA GAA ATA GAA TTG GTA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Ile Glu Leu Val Asn Val Thr Glu
    40                  45                  50

GAT TTT AAC ATG TGG AAA AAT AAA ATG GTA GAC CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Lys Met Val Asp Gln Met
            55                  60

CAT GAG GAT ATA ATC AGT TTA TGG GAT GAA AGC CTA AAG 231
His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser Leu Lys
 65                  70                  75

CCA TGT GTA AAG TTA ACC CCA CTT TGT GTT ACT CTA AAC 270
Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
        80                  85                  90

TGC AGT GAT GTG AAC AAT TCC ACA AAT CCT AAT GAT ACT 309
Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr
            95                  100

AAT ACT AAT TCC ACT AAT ACT ACT TCC TCT ACT CCT ACG 348
Asn Thr Asn Ser Thr Asn Thr Thr Ser Ser Thr Pro Thr
    105                 110                 115

GCC ACT ACT AGT AGC GAG GAA AAG ATG GAG AAG GGA GAA 387
Ala Thr Thr Ser Ser Glu Glu Lys Met Glu Lys Gly Glu
            120                 125

ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA CAC ATG AAA 426
Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr His Met Lys
130                 135                 140

GAT AAG GCA CAG AAA GAA TAT GCA CTT TTT TAT AAA CTT 465
Asp Lys Ala Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
        145                 150                 155

GAT ATA GTA CCA ATA GAT GAT AAT AAT GCC AGC TAT AGG 504
Asp Ile Val Pro Ile Asp Asp Asn Asn Ala Ser Tyr Arg
                160                 165

TTG ATA AGT TGT AAT ACC TCA GAC ATT ACA CAG GCC TGT 543
Leu Ile Ser Cys Asn Thr Ser Asp Ile Thr Gln Ala Cys
    170                 175                 180

CCA AAG GTG ACC TTT GAG CCA ATT CCC ATA CAT TAT TGT 582
Pro Lys Val Thr Phe Glu Pro Ile Pro Ile His Tyr Cys
            185                 190
```

```
GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG 621
Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys
195                 200                 205

AAG TTC AAT GGA ACA GGA CCA TGT TCA AAG GTC AGC ACA 660
Lys Phe Asn Gly Thr Gly Pro Cys Ser Lys Val Ser Thr
        210                 215                 220

GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 699
Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
                225                 230

CAA CTG TTG TTA AAT GGC AGT CTT GCA GAA GAA GAA GTA 738
Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
    235                 240                 245

GTA ATT AGA TCT GTC AAT TTC ACA GAC AAT GCT AAA ATC 777
Val Ile Arg Ser Val Asn Phe Thr Asp Asn Ala Lys Ile
            250                 255

ATA ATA GTA CAG CTG AAA GAA CCT GTA GCA ATT AAT TGT 816
Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile Asn Cys
260                 265                 270

ACA AGA CCC AAC AAC AAT ACA AGA AAA GGT ATA CAT CTA 855
Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Leu
        275                 280                 285

GGA CCA GGG AGC ACA TTT TAT ACA ACA GGA GAA ATA ATA 894
Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile
            290                 295

GGA GAC ATA AGA AAA GCA TAT TGC AAG ATT AGT AAA GAA 933
Gly Asp Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu
    300                 305                 310

AAA TGG AAT AAC ACT TTA AGA CAG GTA GTT AAA AAA TTA 972
Lys Trp Asn Asn Thr Leu Arg Gln Val Val Lys Lys Leu
            315                 320

AGA GAA CAA TTT GGG AAT AAA ACA ATA ATT TTT AAT CGA 1011
Arg Glu Gln Phe Gly Asn Lys Thr Ile Ile Phe Asn Arg
325                 330                 335

TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT 1050
Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe
        340                 345                 350

AAC TGT GGA GGG GAG TTT TTC TAC TGT AAT ACA ACA CAA 1089
Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Gln
                355                 360

CTG TTT AAT AGT ACT TGG AAT AAT ACT GAA GGG ACA AAT 1128
Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr Asn
    365                 370                 375

AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167
Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg
            380                 385

ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA AAA 1206
Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
390                 395                 400
```

```
GCA ACG TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
        405                 410                 415

ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
Ile Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly
                420                 425

GGT AGG AAT GTC ACA AAC AAT ACC GAA ACC TTC AGA CCT 1323
Gly Arg Asn Val Thr Asn Asn Thr Glu Thr Phe Arg Pro
    430                 435                 440

GGA GGA GGA GAC ATG AGG GAC AAT TGG AGA AGT GAA TTA 1362
Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
            445                 450

TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
455                 460                 465

GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAC AGA GAC 1440
Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
        470                 475                 480

AAA AGA GCA GCA CTA GGA GCC TTG TTC CTT GGG TTC TTA 1479
Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
                485                 490

GGA GCA TAA AAG CTT CTA GA 1499
Gly Ala Xaa Lys Leu Leu
    495             499
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 499 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala
 1               5                  10                  15

Ser Asp Ala Lys Ala Tyr Asp Thr Gly Val His Asn Val Trp Ala
            20                  25                  30

Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Ile Glu
        35                  40                  45

Leu Val Asn Val Thr Glu Asp Phe Asn Met Trp Lys Asn Lys Met
    50                  55                  60

Val Asp Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser
65                  70                  75

Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
            80                  85                  90

Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr Asn Thr
        95                  100                 105

Asn Ser Thr Asn Thr Thr Ser Ser Thr Pro Thr Ala Thr Thr Ser
    110                 115                 120

Ser Glu Glu Lys Met Glu Lys Gly Glu Ile Lys Asn Cys Ser Phe
125                 130                 135
```

Asn Ile Thr Thr His Met Lys Asp Lys Ala Gln Lys Glu Tyr Ala
140 145 150

Leu Phe Tyr Lys Leu Asp Ile Val Pro Ile Asp Asp Asn Asn Ala
155 160 165

Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Asp Ile Thr Gln Ala
170 175 180

Cys Pro Lys Val Thr Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
185 190 195

Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys Phe Asn
200 205 210

Gly Thr Gly Pro Cys Ser Lys Val Ser Thr Val Gln Cys Thr His
215 220 225

Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser
230 235 240

Leu Ala Glu Glu Glu Val Val Ile Arg Ser Val Asn Phe Thr Asp
245 250 255

Asn Ala Lys Ile Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile
260 265 270

Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Leu
275 280 285

Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile Gly Asp
290 295 300

Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu Lys Trp Asn Asn
305 310 315

Thr Leu Arg Gln Val Val Lys Lys Leu Arg Glu Gln Phe Gly Asn
320 325 330

Lys Thr Ile Ile Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile
335 340 345

Val Met His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn
350 355 360

Thr Thr Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr
365 370 375

Asn Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg Ile
380 385 390

Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Thr Tyr
395 400 405

Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys Ile Ser Asn Ile Thr
410 415 420

Gly Leu Leu Leu Thr Arg Asp Gly Gly Arg Asn Val Thr Asn Asn
425 430 435

Thr Glu Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
440 445 450

Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu
455 460 465

```
Gly Ile Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
                470                 475                 480

Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala
                485                 490                 495

Xaa Lys Leu Leu
            499
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1499 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
GAG GTA CCT GTA TGG AAA GAA GCA ACC ACT ACT CTA 36
Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
  1               5                  10

TTT TGT GCA TCA GAT GCT AAA GCA TAT GAC ACA GAG GTG 75
Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
        15                  20                  25

CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC 114
His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
                30                  35

CCC AAC CCA CAA GAA ATA GAA TTG GTA AAT GTG ACA GAA 153
Pro Asn Pro Gln Glu Ile Glu Leu Val Asn Val Thr Glu
    40                  45                  50

GAT TTT AAC ATG TGG AAA AAT AAA ATG GTA GAC CAG ATG 192
Asp Phe Asn Met Trp Lys Asn Lys Met Val Asp Gln Met
            55                  60

CAT GAG GAT ATA ATC AGT TTA TGG GAT GAA AGC CTA AAG 231
His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser Leu Lys
 65                  70                  75

CCA TGT GTA AAG TTA ACC CCA CTT TGT GTT ACT CTA AAC 270
Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
        80                  85                  90

TGC AGT GAT GTG AAC AAT TCC ACA AAT CCT AAT GAT ACT 309
Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr
                95                  100

AAT ACT AAT TCC ACT AAT ACT ACT TCC TCT ACT CCT ACG 348
Asn Thr Asn Ser Thr Asn Thr Thr Ser Ser Thr Pro Thr
    105                 110                 115

GCC ACT ACT AGT AGC GAG GAA AAG ATG GAG AAG GGA GAA 387
Ala Thr Thr Ser Ser Glu Glu Lys Met Glu Lys Gly Glu
            120                 125

ATA AAA AAC TGC TCT TTC AAT ATC ACC ACA CAC ATG AAA 426
Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr His Met Lys
130                 135                 140

GAT AAG GTA CAG AAA GAA TAT GCA CTT TTT TAT AAA CTT 465
Asp Lys Val Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu
        145                 150                 155
```

```
GAT ATA GTA CCA ATA GAT GAT AAT AAT ACC AGC TAT AGG 504
Asp Ile Val Pro Ile Asp Asp Asn Asn Thr Ser Tyr Arg
                160                 165

TTG ATA AGT TGT AAT ACC TCA GTC ATT ACA CAG GCC TGT 543
Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
    170                 175                 180

CCA ATG GTG ACC TTT GAG CCA ATT CCC ATA CAT TAT TGT 582
Pro Met Val Thr Phe Glu Pro Ile Pro Ile His Tyr Cys
            185                 190

GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAA GAT AAG 621
Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys
195                 200                 205

AAG TTC AAT GGA ACA GGA CCA TGT TCA AAG GTC AGC ACA 660
Lys Phe Asn Gly Thr Gly Pro Cys Ser Lys Val Ser Thr
        210                 215                 220

GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 699
Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
                225                 230

CAA CTG TTG TTA AAT GGC AGT CTT GCA GAA GAA GAA GTA 738
Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
    235                 240                 245

GTA ATT AGA TCT GTC AAT TTC ACA GAC AAT GCT AAA ATC 777
Val Ile Arg Ser Val Asn Phe Thr Asp Asn Ala Lys Ile
            250                 255

ATA ATA GTA CAG CTG AAA GAA CCT GTA GCA ATT AAT TGT 816
Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile Asn Cys
260                 265                 270

ACA AGA CCC AAC AAC AAT ACA AGA AAA GGT ATA CAT CTA 855
Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Leu
        275                 280                 285

GGA CCA GGG AGC ACA TTT TAT ACA ACA GGA GAA ATA ATA 894
Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile
                290                 295

GGA GAC ATA AGA AAA GCA TAT TGC AAG ATT AGT AAA GAA 933
Gly Asp Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu
    300                 305                 310

AAA TGG AAT AAC ACT TTA AGA CAG GTA GTT AAA AAA TTA 972
Lys Trp Asn Asn Thr Leu Arg Gln Val Val Lys Lys Leu
            315                 320

AGA GAA CAA TTT GGG AAT AAA ACA ATA ATT TTT AAT CGA 1011
Arg Glu Gln Phe Gly Asn Lys Thr Ile Ile Phe Asn Arg
325                 330                 335

TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT 1050
Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe
        340                 345                 350

AAC TGT GGA GGG GAG TTT TTC TAC TGT AAT ACA ACA CAA 1089
Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Gln
                355                 360
```

```
CTG TTT AAT AGT ACT TGG AAT AAT ACT GAA GGG ACA AAT 1128
Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr Asn
    365                 370                 375

AGC ACT GAA GGA AAT AGC ACA ATC ACA CTC CCA TGC AGA 1167
Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg
            380                 385

ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA AAA 1206
Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
390                 395                 400

GCA ACG TAT GCC CCT CCC ATC AGA GGA CGA ATT AGA TGC 1245
Ala Thr Tyr Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys
        405                 410                 415

ATA TCA AAT ATT ACA GGA CTG CTA TTA ACA AGA GAT GGT 1284
Ile Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly
                420                 425

GGT AGG AAT GTC ACA AAC AAT ACC GAN NCC TTC AGA CCT 1323
Gly Arg Asn Val Thr Asn Asn Thr Xaa Xaa Phe Arg Pro
    430                 435                 440

GGA GGA GGA GAC ATG AGG GAC AAT TGG AGA AGT GAA TTA 1362
Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu
            445                 450

TAT AAA TAT AAA GTA GTA AAA GTT GAA CCA TTA GGA ATA 1401
Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu Gly Ile
455                 460                 465

GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAC AGA GAC 1440
Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
        470                 475                 480

AAA AGA GCA GCA CTA GGA GCT TTG TTC CTT GGG TTC TTA 1479
Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu
                485                 490

GGA GCA TAA AAG CTT CTA GA 1499
Gly Ala Xaa Lys Leu Leu
    495             499
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 499 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala
 1               5                  10                  15

Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala
            20                  25                  30

Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Ile Glu
        35                  40                  45

Leu Val Asn Val Thr Glu Asp Phe Asn Met Trp Lys Asn Lys Met
    50                  55                  60

Val Asp Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Glu Ser
65                  70                  75
```

```
Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn
                80                  85                  90

Cys Ser Asp Val Asn Asn Ser Thr Asn Pro Asn Asp Thr Asn Thr
            95                  100                 105

Asn Ser Thr Asn Thr Thr Ser Ser Thr Pro Thr Ala Thr Thr Ser
        110                 115                 120

Ser Glu Glu Lys Met Glu Lys Gly Glu Ile Lys Asn Cys Ser Phe
    125                 130                 135

Asn Ile Thr Thr His Met Lys Asp Lys Val Gln Lys Glu Tyr Ala
140                 145                 150

Leu Phe Tyr Lys Leu Asp Ile Val Pro Ile Asp Asp Asn Asn Thr
155                 160                 165

Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala
170                 175                 180

Cys Pro Met Val Thr Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
185                 190                 195

Pro Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys Phe Asn
200                 205                 210

Gly Thr Gly Pro Cys Ser Lys Val Ser Thr Val Gln Cys Thr His
215                 220                 225

Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser
230                 235                 240

Leu Ala Glu Glu Glu Val Val Ile Arg Ser Val Asn Phe Thr Asp
245                 250                 255

Asn Ala Lys Ile Ile Ile Val Gln Leu Lys Glu Pro Val Ala Ile
260                 265                 270

Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Gly Ile His Leu
275                 280                 285

Gly Pro Gly Ser Thr Phe Tyr Thr Thr Gly Glu Ile Ile Gly Asp
290                 295                 300

Ile Arg Lys Ala Tyr Cys Lys Ile Ser Lys Glu Lys Trp Asn Asn
305                 310                 315

Thr Leu Arg Gln Val Val Lys Lys Leu Arg Glu Gln Phe Gly Asn
320                 325                 330

Lys Thr Ile Ile Phe Asn Arg Ser Ser Gly Gly Asp Pro Glu Ile
335                 340                 345

Val Met His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn
350                 355                 360

Thr Thr Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Glu Gly Thr
365                 370                 375

Asn Ser Thr Glu Gly Asn Ser Thr Ile Thr Leu Pro Cys Arg Ile
380                 385                 390

Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Thr Tyr
395                 400                 405
```

```
Ala Pro Pro Ile Arg Gly Arg Ile Arg Cys Ile Ser Asn Ile Thr
                410                 415                 420

Gly Leu Leu Leu Thr Arg Asp Gly Gly Arg Asn Val Thr Asn Asn
                425                 430                 435

Thr Xaa Xaa Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
                440                 445                 450

Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Val Glu Pro Leu
                455                 460                 465

Gly Ile Ala Pro Thr Lys Ala Lys Arg Arg Val Val His Arg Asp
                470                 475                 480

Lys Arg Ala Ala Leu Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala
                485                 490                 495

Xaa Lys Leu Leu
            499
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1475 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
G   GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
    Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
      1               5                  10

TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
         15                  20                  25

AAT GTT TGG GCA ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                 30                  35

AAC CCA CAA GAA ATA GTA TTG GGA AAT GTG ACA GAA AAT 154
Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
     40                  45                  50

TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
             55                  60

GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro
 65                  70                  75

TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
         80                  85                  90

AAG GAT CTG GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
                 95                 100

ACC AAT AAT AGT AGT TTG GAG GGA CTA AGA GAA CAA ATG 349
Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
    105                 110                 115
```

```
ACA AAC TGC TCT TTC AAC ATC ACC ACA AGT ATA AGA GAT 388
Thr A n Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
          120                 125

AAG GTG CAG AAA GAA TAT GCA CTT TTG TAT AAA CTT GAT 427
Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
130                 135                 140

GTA GTA CCA ATA GAA GAA GAT GAC AAT ACT AGC TAT AGA 466
Val Val Pro Ile Glu Glu Asp Asp Asn Thr Ser Tyr Arg
        145                 150                 155

TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCT TGT 505
Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
                160                 165

CCA AAG ACA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT 544
Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
    170                 175                 180

GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG 583
Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys
          185                 190

AAG TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGC ACA 622
Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr
195                 200                 205

GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 661
Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
        210                 215                 220

CAA CTG TTG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTA 700
Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
                225                 230

GTA ATC AGA TCT GCC AAT TTC ACA GAC AAT GCT AAA ACC 739
Val Ile Arg Ser Ala Asn Phe Thr Asp Asn Ala Lys Thr
    235                 240                 245

ATA ATA GTA CAT CTA AAT GAA ACT GTA AAA ATT AAT TGT 778
Ile Ile Val His Leu Asn Glu Thr Val Lys Ile Asn Cys
          250                 255

ACA AGA CTT GGC AAC AAT ACA AGA AAA AGT ATA AAT ATA 817
Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile Asn Ile
260                 265                 270

GGA CCA GGG AGA GTA CTC TAT GCA ACA GGA GAA ATA ATA 856
Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile
        275                 280                 285

GGA GAC ATA AGA CAA GCA CAT TGT AAC ATT AGT AGA GCA 895
Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala
                290                 295

CAA TGG AAT AAG ACT TTA GAA AAG GTA GTT GAC AAA TTA 934
Gln Trp Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu
    300                 305                 310

AGA AAA CAA TTT GGG GAT AAT ACA ACA ATA GCT TTT AAT 973
Arg Lys Gln Phe Gly Asp Asn Thr Thr Ile Ala Phe Asn
          315                 320
```

```
CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC ACT 1012
Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Thr
325                 330                 335

TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA 1051
Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr
        340                 345                 350

CAA CTG TTT AAT AGT ACT TGG AAT AAT ACT TGG AAG GAT 1090
Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Trp Lys Asp
                355                 360

CCT AAC AGG AGT GAC AAT ATC ACA CTC CCA TGC AGA ATA 1129
Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg Ile
    365                 370                 375

AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA 1168
Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala
            380                 385

ATG TAC GCC CCT CCC ATC AGA GGG GAA ATT AGA TGT TCA 1207
Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser
390                 395                 400

TCA AAT ATC ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT 1246
Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly
        405                 410                 415

AAT GAC GAT GGT AAT GAC ACG ACC ACA AAC AGG ACC GAG 1285
Asn Asp Asp Gly Asn Asp Thr Thr Thr Asn Arg Thr Glu
                420                 425

ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1324
Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
    430                 435                 440

AGA AGT GAA TTA TAT AGA TAT AAA GTA GTA AAA ATT GAA 1363
Arg Ser Glu Leu Tyr Arg Tyr Lys Val Val Lys Ile Glu
            445                 450

CCA TTA GGA ATA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1402
Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg Arg Val
455                 460                 465

GTG CAG AGA GAA AAA AGA GCA GTA GGA CTA GGA GCT TTG 1441
Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
        470                 475                 480

TTC CTT GGG T TCTTAGGAG CATAAAGCTT CTAGA 1475
Phe Leu Gly
        483
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 491 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe Cys Ala Ser
 1               5                  10                  15

Asp Ala Lys Ala Tyr Asp Arg Glu Val His Asn Val Trp Ala Thr
            20                  25                  30
```

His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Ile Val Leu
35 40 45

Gly Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val
50 55 60

Glu Gln Met His Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu
65 70 75

Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
80 85 90

Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile Thr Asn
95 100 105

Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met Thr Asn Cys Ser
110 115 120

Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Val Gln Lys Glu Tyr
125 130 135

Ala Leu Leu Tyr Lys Leu Asp Val Val Pro Ile Glu Glu Asp Asp
140 145 150

Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr
155 160 165

Gln Ala Cys Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr
170 175 180

Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys
185 190 195

Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val Gln Cys
200 205 210

Thr His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn
215 220 225

Gly Ser Leu Ala Glu Glu Glu Val Val Ile Arg Ser Ala Asn Phe
230 235 240

Thr Asp Asn Ala Lys Thr Ile Ile Val His Leu Asn Glu Thr Val
245 250 255

Lys Ile Asn Cys Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile
260 265 270

Asn Ile Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile
275 280 285

Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala Gln Trp
290 295 300

Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu Arg Lys Gln Phe
305 310 315

Gly Asp Asn Thr Thr Ile Ala Phe Asn Arg Ser Ser Gly Gly Asp
320 325 330

Pro Glu Ile Val Met His Thr Phe Asn Cys Gly Gly Glu Phe Phe
335 340 345

Tyr Cys Asn Thr Thr Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr
350 355 360

```
Trp Lys Asp Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg
                365                 370                 375

Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
            380                 385                 390

Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser Ser Asn Ile
            395                 400                 405

Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn Asp Asp Gly Asn
            410                 415                 420

Asp Thr Thr Thr Asn Arg Thr Glu Ile Phe Arg Pro Gly Gly Gly
            425                 430                 435

Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Arg Tyr Lys Val
            440                 445                 450

Val Lys Ile Glu Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg
            455                 460                 465

Arg Val Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
            470                 475                 480

Phe Leu Gly Phe Leu Gly Ala Leu Phe Leu Gly
            485                 490 491
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1475 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
G   GTA CCT GTG TGG AAA GAA GCA AAC ACA ACT CTA TTT 37
    Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe
      1               5                  10

TGT GCA TCA GAT GCT AAA GCA TAT GAT AGA GAA GTA CAT 76
Cys Ala Ser Asp Ala Lys Ala Tyr Asp Arg Glu Val His
         15                  20                  25

AAT GTT TGG GCA ACA CAT GCC TGT GTA CCC ACA GAC CCC 115
Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro
                 30                  35

AAC CCA CAA GAA ATA GTA TTG GGA AAT GTG ACA GAA AAT 154
Asn Pro Gln Glu Ile Val Leu Gly Asn Val Thr Glu Asn
     40                  45                  50

TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAA ATG CAT 193
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
             55                  60

GAG GAT ATA ATC AAT TTA TGG GAT CAA AGC TTA AAG CCA 232
Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu Lys Pro
 65                  70                  75

TGT GTA AAG TTA ACT CCA CTC TGT GTT ACT TTA AAG TGC 271
Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
         80                  85                  90
```

```
AAG GAT CTG GAG AGG AAT ACT ACC TAT AAT AGC ACT ATT 310
Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile
                95                  100

ACC AAT AAT AGT AGT TTG GAG GGA CTA AGA GAA CAA ATG 349
Thr Asn Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met
    105                 110                 115

ACA AAC TGC TCT TTC AAC ATC ACC ACA AGT ATA AGA GAT 388
Thr Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp
            120                 125

AAG GTG CAG AAA GAA TAT GCA CTT TTG TAT AAA CTT GAT 427
Lys Val Gln Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp
130                 135                 140

GTA GTA CCA ATA GAA GAA GAT GAC AAT ACT AGC TAT AGA 466
Val Val Pro Ile Glu Glu Asp Asp Asn Thr Ser Tyr Arg
        145                 150                 155

TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCT TGT 505
Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
            160                 165

CCA AAG ACA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT 544
Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
    170                 175                 180

GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAT GAT AAG 583
Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys
            185                 190

AAG TTC AAT GGA ACA GGA CCA TGT AAA AAT GTC AGC ACA 622
Lys Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr
195                 200                 205

GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT 661
Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
        210                 215                 220

CAA CTG TTG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTA 700
Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val
            225                 230

GTA ATC AGA TCT GCC AAT TTC ACA GAC AAT GCT AAA ACC 739
Val Ile Arg Ser Ala Asn Phe Thr Asp Asn Ala Lys Thr
    235                 240                 245

ATA ATA GTA CAT CTA AAT GAA ACT GTA AAA ATT AAT TGT 778
Ile Ile Val His Leu Asn Glu Thr Val Lys Ile Asn Cys
            250                 255

ACA AGA CTT GGC AAC AAT ACA AGA AAA AGT ATA AAT ATA 817
Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile Asn Ile
260                 265                 270

GGA CCA GGG AGA GTA CTC TAT GCA ACA GGA GAA ATA ATA 856
Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile
        275                 280                 285

GGA GAC ATA AGA CAA GCA CAT TGT AAC ATT AGT AGA GCA 895
Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala
            290                 295
```

```
CAA TGG AAT AAG ACT TTA GAA AAG GTA GTT GAC AAG TTA 934
Gln Trp Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu
    300                 305                 310

AGA AAA CAA TTT GGG GAT AAT ACA ACA ATA GCT TTT AAT 973
Arg Lys Gln Phe Gly Asp Asn Thr Thr Ile Ala Phe Asn
            315                 320

CGA TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC ACT 1012
Arg Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Thr
325                 330                 335

TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA 1051
Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr
        340                 345                 350

CAA CTG TTT AAT AGT ACT TGG AAT AAT ACT TGG AAG GAT 1090
Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Trp Lys Asp
                355                 360

CCT AAC AGG AGT GAC AAT ATC ACA CTC CCA TGC AGA ATA 1129
Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg Ile
    365                 370                 375

AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA GCA 1168
Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala
            380                 385

ATG TAC GCC CCT CCC ATC AGA GGG GAA ATT AGA TGT TCA 1207
Met Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser
390                 395                 400

TCA AAT ATC ACA GGG CTG CTA CTA ACA AGA GAT GGT GGT 1246
Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly
        405                 410                 415

AAT GAC GAT GGT AAT GAC ACG ACC ACA AAC AGG ACC GAG 1285
Asn Asp Asp Gly Asn Asp Thr Thr Thr Asn Arg Thr Glu
                420                 425

ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1324
Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
    430                 435                 440

AGA AGT GAA TTA TAT AGA TAT AAA GTA GTA AAA ATT GAA 1363
Arg Ser Glu Leu Tyr Arg Tyr Lys Val Val Lys Ile Glu
            445                 450

CCA TTA GGA ATA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1402
Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg Arg Val
455                 460                 465

GTG CAG AGA GAA AAA AGA GCA GTA GGA CTA GGA GCT TTG 1441
Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
        470                 475                 480

TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1475
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
                485                 490 491
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 491 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe Cys Ala Ser
1 5 10 15

Asp Ala Lys Ala Tyr Asp Arg Glu Val His Asn Val Trp Ala Thr
20 25 30

His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Ile Val Leu
35 40 45

Gly Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val
50 55 60

Glu Gln Met His Glu Asp Ile Ile Asn Leu Trp Asp Gln Ser Leu
65 70 75

Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Lys Cys
80 85 90

Lys Asp Leu Glu Arg Asn Thr Thr Tyr Asn Ser Thr Ile Thr Asn
95 100 105

Asn Ser Ser Leu Glu Gly Leu Arg Glu Gln Met Thr Asn Cys Ser
110 115 120

Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Val Gln Lys Glu Tyr
125 130 135

Ala Leu Leu Tyr Lys Leu Asp Val Val Pro Ile Glu Glu Asp Asp
140 145 150

Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr
155 160 165

Gln Ala Cys Pro Lys Thr Ser Phe Glu Pro Ile Pro Ile His Tyr
170 175 180

Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys
185 190 195

Phe Asn Gly Thr Gly Pro Cys Lys Asn Val Ser Thr Val Gln Cys
200 205 210

Thr His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn
215 220 225

Gly Ser Leu Ala Glu Glu Glu Val Val Ile Arg Ser Ala Asn Phe
230 235 240

Thr Asp Asn Ala Lys Thr Ile Ile Val His Leu Asn Glu Thr Val
245 250 255

Lys Ile Asn Cys Thr Arg Leu Gly Asn Asn Thr Arg Lys Ser Ile
260 265 270

Asn Ile Gly Pro Gly Arg Val Leu Tyr Ala Thr Gly Glu Ile Ile
275 280 285

Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Arg Ala Gln Trp
290 295 300

Asn Lys Thr Leu Glu Lys Val Val Asp Lys Leu Arg Lys Gln Phe
305 310 315

```
Gly Asp Asn Thr Thr Ile Ala Phe Asn Arg Ser Ser Gly Gly Asp
                320                 325                 330

Pro Glu Ile Val Met His Thr Phe Asn Cys Gly Gly Glu Phe Phe
                335                 340                 345

Tyr Cys Asn Thr Thr Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr
                350                 355                 360

Trp Lys Asp Pro Asn Arg Ser Asp Asn Ile Thr Leu Pro Cys Arg
                365                 370                 375

Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
                380                 385                 390

Tyr Ala Pro Pro Ile Arg Gly Glu Ile Arg Cys Ser Ser Asn Ile
                395                 400                 405

Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn Asp Asp Gly Asn
                410                 415                 420

Asp Thr Thr Thr Asn Arg Thr Glu Ile Phe Arg Pro Gly Gly Gly
                425                 430                 435

Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Arg Tyr Lys Val
                440                 445                 450

Val Lys Ile Glu Pro Leu Gly Ile Ala Pro Thr Arg Ala Lys Arg
                455                 460                 465

Arg Val Val Gln Arg Glu Lys Arg Ala Val Gly Leu Gly Ala Leu
                470                 475                 480

Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
                485                 490 491
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1435 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
   CTC GAG GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT 36
   Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
     1               5                  10

CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT TCA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu
        15                  20                  25

GCA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA 114
Ala His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
                30                  35

GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr
     40                  45                  50

GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
             55                  60
```

```
ATG CAT GGG GAT ATA ATT AGT TTA TGG GAT CAA AGC CTA 231
Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65                  70                  75

AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACG TTA 270
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
         80                  85                  90

AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309
Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
                95                 100

ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 348
Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
    105                 110                 115

ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
            120                 125

CTT TTT TAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
130                 135                 140

AAT ACT AGC TAT AGG TTG ATA AGT TGT AAC ACC TCA GTC 465
Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
        145                 150                 155

ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
            160                 165

CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT CTA 543
Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
    170                 175                 180

AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
            185                 190

ACA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
195                 200                 205

CCA GTA GTA TCA ACT CAA CTG TTG TTA AAT GGC AGT CTA 660
Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
        210                 215                 220

GCA GAA GAA GAC ATA GTA ATT AGA TCC GCC AAT CTC ACA 699
Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
                225                 230

GAC AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 738
Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser
    235                 240                 245

GTA ACA ATG AAT TGT ACA AGA CCC AAC AAC AAT ACA ATG 777
Val Thr Met Asn Cys Thr Arg Pro Asn Asn Asn Thr Met
            250                 255

AAA AGT ATA CAT ATA GGA CCA GGC AGA GCA TTT TAT GCA 816
Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala
260                 265                 270
```

```
ACA GGA AAC ATA ATA GGA GAT ATA AGA CAA GCA CAT TGT 855
Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys
      275                 280                 285

AAC ATT AGT GGA ACA AAA TGG AAT GAC ACT TTG AAA AAG 894
Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys
            290                 295

ATA GCT ATA AAA TTA AGA GAA CAA TTT AAT AAG ACA ATA 933
Ile Ala Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile
    300                 305                 310

GTC TTT AAT CAA TCC TCA GGA GGG GAC CCA GAA ATT GCA 972
Val Phe Asn Gln Ser Ser Gly Gly Asp Pro Glu Ile Ala
          315                 320

ACG CTC AGT TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT 1011
Thr Leu Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys
325                 330                 335

AAT TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT AGT ACT 1050
Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Ser Thr
      340                 345                 350

GGG TCA AAT AAC ACT AAA GGA AAT GAC ACA ATC ACA CTC 1089
Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr Ile Thr Leu
            355                 360

CCA TGC AGA ATA AGA CAA ATT ATA AAC ATG TGG CAG AAA 1128
Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln Lys
    365                 370                 375

ATA GGA AAA GCA ATG TAT GCC CCT CCC ATC AAA GGG CAA 1167
Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln
          380                 385

ATT AGA TGT TCA TCA AAT ATT ACA GGG CTA ATA TTA ACA 1206
Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr
390                 395                 400

AGA GAT GGT GGT AAC AAC AAC ATG AGC AAG ACC ACC GAG 1245
Arg Asp Gly Gly Asn Asn Asn Met Ser Lys Thr Thr Glu
      405                 410                 415

ACC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1284
Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
            420                 425

AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT GAA 1323
Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
    430                 435                 440

CCA TTA GGA GTA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1362
Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val
          445                 450

GTG CAG AGA GAA AAA AGA GCA GTG GGA ATA GGA GCT GTG 1401
Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Val
455                 460                 465

TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1435
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
      470                 475         478
```

(2) INFORMATION FOR SEQ ID NO:26:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 478 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys
1 5 10 15

Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu Ala His Asn Val Trp
20 25 30

Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val
35 40 45

Glu Leu Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn
50 55 60

Met Val Glu Gln Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln
65 70 75

Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
80 85 90

Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr Ile Glu
95 100 105

Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Asn Ile
110 115 120

Arg Asp Arg Phe Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu Asp
125 130 135

Val Ile Pro Leu Gly Asn Asp Asn Thr Ser Tyr Arg Leu Ile Ser
140 145 150

Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro Lys Val Ser Phe
155 160 165

Glu Pro Ile Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile
170 175 180

Leu Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Thr
185 190 195

Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys Pro Val Val
200 205 210

Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Asp Ile
215 220 225

Val Ile Arg Ser Ala Asn Leu Thr Asp Asn Ala Lys Asn Ile Ile
230 235 240

Val Gln Leu Asn Glu Ser Val Thr Met Asn Cys Thr Arg Pro Asn
245 250 255

Asn Asn Thr Met Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe
260 265 270

Tyr Ala Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys
275 280 285

```
Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys Ile Ala
290                 295                 300

Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile Val Phe Asn Gln
305                 310                 315

Ser Ser Gly Gly Asp Pro Glu Ile Ala Thr Leu Ser Phe Asn Cys
320                 325                 330

Gly Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Leu Phe Asn Ser
335                 340                 345

Thr Trp Asn Ser Thr Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr
350                 355                 360

Ile Thr Leu Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln
365                 370                 375

Lys Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln Ile
380                 385                 390

Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr Arg Asp Gly
395                 400                 405

Gly Asn Asn Asn Met Ser Lys Thr Thr Glu Thr Phe Arg Pro Gly
410                 415                 420

Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys Tyr
425                 430                 435

Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr Arg Ala
440                 445                 450

Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly
455                 460                 465

Ala Val Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
470                 475         478
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1435 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
CTC GAG GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT 36
Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr
 1               5                  10

CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT TCA GAG 75
Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu
        15                  20                  25

GCA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA 114
Ala His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr
                30                  35

GAC CCC AAC CCA CAA GAA GTA GAA TTG GAA AAT GTG ACA 153
Asp Pro Asn Pro Gln Glu Val Glu Leu Glu Asn Val Thr
    40                  45                  50
```

```
GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG 192
Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln
          55                  60

ATG CAT GGG GAT ATA ATT AGT TTA TGG GAT CAA AGC CTA 231
Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
 65                  70                  75

AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACG TTA 270
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
        80                  85                  90

AAT TGC ACT GAC CCA AAT GTT ACT AAT AGC GAG AGA ACG 309
Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr
                95                  100

ATA GAG GGG GGA GAA ATA AAA AAT TGC TCT TTC AAT ATC 348
Ile Glu Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile
    105                 110                 115

ACC ACA AAC ATA AGA GAT AGG TTT CAG AAA GAA TAT GCA 387
Thr Thr Asn Ile Arg Asp Arg Phe Gln Lys Glu Tyr Ala
            120                 125

CTT TTT TAT AAA CTT GAT GTA ATA CCA TTA GGT AAT GAT 426
Leu Phe Tyr Lys Leu Asp Val Ile Pro Leu Gly Asn Asp
130                 135                 140

AAT ACT AGC TAT AGG TTG ATA AGT TGT AAC ACC TCA GTC 465
Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val
        145                 150                 155

ATT ACA CAG GCC TGT CCA AAG GTA TCC TTT GAG CCA ATT 504
Ile Thr Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile
                160                 165

CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT CTA 543
Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu
    170                 175                 180

AAG TGT AAA GAT AAG AAG TTC AAT GGA ACA GGA CCA TGT 582
Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys
            185                 190

ACA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AAG 621
Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys
195                 200                 205

CCA GTA GTA TCA ACT CAA CTG TTG TTA AAT GGC AGT CTA 660
Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu
        210                 215                 220

GCA GAA GAA GAC ATA GTA ATT AGA TCC GCC AAT CTC ACA 699
Ala Glu Glu Asp Ile Val Ile Arg Ser Ala Asn Leu Thr
                225                 230

GAC AAT GCT AAA AAC ATA ATA GTA CAG CTG AAT GAA TCT 738
Asp Asn Ala Lys Asn Ile Ile Val Gln Leu Asn Glu Ser
    235                 240                 245

GTA ACA ATG AAT TGT ACA AGA CCC AAC AAC AAT ACA ATG 777
Val Thr Met Asn Cys Thr Arg Pro Asn Asn Asn Thr Met
            250                 255
```

```
AAA AGT ATA CAT ATA GGA CCA GGC AGA GCA TTT TAT GCA 816
Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala
260                 265                 270

ACA GGA AAC ATA ATA GGA GAT ATA AGA CAA GCA CAT TGT 855
Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys
        275                 280                 285

AAC ATT AGT GGA ACA AAA TGG AAT GAC ACT TTG AAA AAG 894
Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys
                290                 295

ATA GCT ATA AAA TTA AGA GAA CAA TTT AAT AAG ACA ATA 933
Ile Ala Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile
    300                 305                 310

GTC TTT AAT CAA TCC TCA GGA GGG GAC CCA GAA ATT GCA 972
Val Phe Asn Gln Ser Ser Gly Gly Asp Pro Glu Ile Ala
            315                 320

ACG CTC AGT TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT 1011
Thr Leu Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys
325                 330                 335

AAT TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT AGT ACT 1050
Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Ser Thr
        340                 345                 350

GGG TCA AAT AAC ACT AAA GGA AAT GAC ACA ATC ACA CTC 1089
Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr Ile Thr Leu
                355                 360

CCA TGC AGA ATA AGA CAA ATT ATA AAC ATG TGG CAG AAA 1128
Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln Lys
    365                 370                 375

ATA GGA AAA GCA ATG TAT GCC CCT CCC ATC AAA GGG CAA 1167
Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln
            380                 385

ATT AGA TGT TCA TCA AAT ATT ACA GGG CTA ATA TTA ACA 1206
Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr
390                 395                 400

AGA GAT GGT GGT AAC AAC AAC ATG AGC AAG ACC ACC GAG 1245
Arg Asp Gly Gly Asn Asn Asn Met Ser Lys Thr Thr Glu
        405                 410                 415

ACC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT TGG 1284
Thr Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp
                420                 425

AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA AAA ATT GAA 1323
Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu
    430                 435                 440

CCA TTA GGA GTA GCA CCC ACC AGG GCA AAG AGA AGA GTG 1362
Pro Leu Gly Val Ala Pro Thr Arg Ala Lys Arg Arg Val
            445                 450

GTG CAG AGA GAA AAA AGA GCA GTG GGA ATA GGA GCT GTG 1401
Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala Val
455                 460                 465
```

```
TTC CTT GGG TTC TTG GGA GCA TAA AGC TTC TAG A 1435
Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
470 475 478
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 478 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Leu Glu Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys
1 5 10 15

Ala Ser Asp Ala Lys Ala Tyr Asp Ser Glu Ala His Asn Val Trp
20 25 30

Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val
35 40 45

Glu Leu Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn
50 55 60

Met Val Glu Gln Met His Gly Asp Ile Ile Ser Leu Trp Asp Gln
65 70 75

Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
80 85 90

Asn Cys Thr Asp Pro Asn Val Thr Asn Ser Glu Arg Thr Ile Glu
95 100 105

Gly Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Asn Ile
110 115 120

Arg Asp Arg Phe Gln Lys Glu Tyr Ala Leu Phe Tyr Lys Leu Asp
125 130 135

Val Ile Pro Leu Gly Asn Asp Asn Thr Ser Tyr Arg Leu Ile Ser
140 145 150

Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro Lys Val Ser Phe
155 160 165

Glu Pro Ile Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile
170 175 180

Leu Lys Cys Lys Asp Lys Lys Phe Asn Gly Thr Gly Pro Cys Thr
185 190 195

Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Lys Pro Val Val
200 205 210

Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Asp Ile
215 220 225

Val Ile Arg Ser Ala Asn Leu Thr Asp Asn Ala Lys Asn Ile Ile
230 235 240

Val Gln Leu Asn Glu Ser Val Thr Met Asn Cys Thr Arg Pro Asn
245 250 255

Asn Asn Thr Met Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe
260 265 270
```

```
Tyr Ala Thr Gly Asn Ile Ile Gly Asp Ile Arg Gln Ala His Cys
                275                 280                 285

Asn Ile Ser Gly Thr Lys Trp Asn Asp Thr Leu Lys Lys Ile Ala
            290                 295                 300

Ile Lys Leu Arg Glu Gln Phe Asn Lys Thr Ile Val Phe Asn Gln
        305                 310                 315

Ser Ser Gly Gly Asp Pro Glu Ile Ala Thr Leu Ser Phe Asn Cys
    320                 325                 330

Gly Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Leu Phe Asn Ser
335                 340                 345

Thr Trp Asn Ser Thr Gly Ser Asn Asn Thr Lys Gly Asn Asp Thr
            350                 355                 360

Ile Thr Leu Pro Cys Arg Ile Arg Gln Ile Ile Asn Met Trp Gln
        365                 370                 375

Lys Ile Gly Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln Ile
    380                 385                 390

Arg Cys Ser Ser Asn Ile Thr Gly Leu Ile Leu Thr Arg Asp Gly
395                 400                 405

Gly Asn Asn Asn Met Ser Lys Thr Thr Glu Thr Phe Arg Pro Gly
            410                 415                 420

Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys Tyr
        425                 430                 435

Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr Arg Ala
    440                 445                 450

Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly
455                 460                 465

Ala Val Phe Leu Gly Phe Leu Gly Ala Xaa Ser Phe Xaa
            470                 475         478
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 511 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
Met Arg Val Lys Gly Ile Arg Arg Asn Tyr Gln His Trp Trp Gly Arg
1               5                   10                  15

Gly Thr Met Leu Leu Gly Leu Leu Met Ile Cys Ser Ala Thr Glu Lys
            20                  25                  30

Leu Trp Val Thr Val Tyr Tyr Gly Val Pro Val Trp Lys Glu Ala Thr
        35                  40                  45

Thr Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Ala
    50                  55                  60

His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro
65                  70                  75                  80
```

Gln Glu Val Glu Leu Val Asn Val Thr Glu Asn Phe Asn Met Trp Lys
85 90 95

Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asn
100 105 110

Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
115 120 125

Asn Cys Thr Asp Leu Arg Asn Thr Thr Asn Thr Asn Asn Ser Thr Asp
130 135 140

Asn Asn Asn Ser Lys Ser Glu Gly Thr Ile Lys Gly Gly Glu Met Lys
145 150 155 160

Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Gly Asp Lys Met Gln Lys
165 170 175

Glu Tyr Ala Leu Leu Tyr Lys Leu Asp Ile Glu Pro Ile Asp Asn Asp
180 185 190

Ser Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln
195 200 205

Ala Cys Pro Lys Ile Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
210 215 220

Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys Phe Ser Gly
225 230 235 240

Lys Gly Ser Cys Lys Asn Val Ser Thr Val Gln Cys Thr His Gly Ile
245 250 255

Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
260 265 270

Glu Glu Val Val Ile Arg Ser Glu Asp Phe Thr Asp Asn Ala Lys Thr
275 280 285

Ile Ile Val His Leu Lys Glu Ser Val Gln Ile Asn Cys Thr Arg Pro
290 295 300

Asn Tyr Asn Lys Arg Lys Arg Ile His Ile Gly Pro Gly Arg Ala Phe
305 310 315 320

Tyr Thr Thr Lys Asn Ile Lys Gly Thr Ile Arg Gln Ala His Cys Ile
325 330 335

Ile Ser Arg Ala Lys Trp Asn Asp Thr Leu Arg Gln Ile Val Ser Lys
340 345 350

Leu Lys Glu Gln Phe Lys Asn Lys Thr Ile Val Phe Asn Pro Ser Ser
355 360 365

Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gly Gly Glu
370 375 380

Phe Phe Tyr Cys Asn Thr Ser Pro Leu Phe Asn Ser Ile Trp Asn Gly
385 390 395 400

Asn Asn Thr Trp Asn Asn Thr Thr Gly Ser Asn Asn Asn Ile Thr Leu
405 410 415

Gln Cys Lys Ile Lys Gln Ile Ile Asn Met Trp Gln Lys Val Gly Lys
420 425 430

```
Ala Met Tyr Ala Pro Pro Il  Glu Gly Gln Ile Arg Cys Ser Ser Asn
        435                 440                 445

Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Glu Asp Thr Asp Thr
    450                 455                 460

Asn Asp Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn
465                 470                 475                 480

Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Thr Ile Glu Pro Leu
                485                 490                 495

Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu
            500                 505                 510
```

(2) INFORMATION FOR SEQ ID NO:30

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2800 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
TTCGAGCTCG CCCGACATTG ATTATTGACT AGAGTCGATC GACAGCTGTG     50

GAATGTGTGT CAGTTAGGGT GTGGAAAGTC CCCAGGCTCC CCAGCAGGCA    100

GAAGTATGCA AAGCATGCAT CTCAATTAGT CAGCAACCAG GTGTGGAAAG    150

TCCCCAGGCT CCCCAGCAGG CAGAAGTATG CAAAGCATGC ATCTCAATTA    200

GTCAGCAACC ATAGTCCCGC CCCTAACTCC GCCCATCCCG  CCCCTAACTC   250

CGCCCAGTTC CGCCCATTCT CCGCCCCATG GCTGACTAAT TTTTTTTATT    300

TATGCAGAGG CCGAGGCCGC CTCGGCCTCT GAGCTATTCC AGAAGTAGTG    350

AGGAGGCTTT TTTGGAGGCC TAGGCTTTTG CAAAAAGCTA GCTTATCCGG    400

CCGGGAACGG TGCATTGGAA CGCGGATTCC CCGTGCCAAG AGTCAGGTAA    450

GTACCGCCTA TAGAGTCTAT AGGCCCACCC CCTTGGCTTC GTTAGAACGC    500

GGCTACAATT AATACATAAC CTTTTGGATC GATCCTACTG ACACTGACAT    550

CCACTTTTTC TTTTTCTCCA CAGGTGTCCA CTCCCAGGTC CAACTGCACC    600

TCGGTTCGCG AAGCTAGCTT GGGCTGCATC GATTGAATTC CACTGCCTTC    650

CACCAAGCTC TGCAGGATCC CAGAGTCAGG GG TCT GTA TCT TCC TGC    697
                                     Ser Val Ser Ser Cys
                                      1               5

TGG TGG CTC CAG TTC AGG AAC AGT AAA CCC TGC TCC GAA TAT    739
Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Cys Ser Glu Tyr
            10                  15

TGC CTC TCA CAT CTC GTC AAT CTC CGC GAG GAC TGG GGA CCC    781
Cys Leu Ser His Leu Val Asn Leu Arg Glu Asp Trp Gly Pro
 20                 25                  30
```

```
TCT GAC AAG CTT CAG CGC GAA CGA CCA ACT ACC CCG ATC ATC      823
Cys Asp Lys Leu Gln Arg Glu Arg Pro Thr Thr Pro Ile Ile
 35                  40                  45

AGT TAT CCT TAA GGT CTC TTT TGT GTG GTG CGT TCC GGT ATG      865
Ser Tyr Pro  *  Gly Leu Phe Cys Val Val Arg Ser Gly Met
     50             55                  60

GGG GGG ACT GCC GCC AGG TTG GGG GCC GTG ATT TTG TTT GTC      907
Gly Gly Thr Ala Ala Arg Leu Gly Ala Val Ile Leu Phe Val
 62          65                  70                  75

GTC ATA GTG GGC CTC CAT GGG GTC CGC GGC AAA TAT GCC TTG      949
Val Ile Val Gly Leu His Gly Val Arg Gly Lys Tyr Ala Leu
                 80                  85

GCG GAT GCC TCT CTC AAG ATG GCC GAC CCC AAT CGA TTT CGC      991
Ala Asp Ala Ser Leu Lys Met Ala Asp Pro Asn Arg Phe Arg
 90                  95                 100

GGC AAA GAC CTT CCG GTC CTG GAC CAG CTG CTC GAG GTA CCT     1033
Gly Lys Asp Leu Pro Val Leu Asp Gln Leu Leu Glu Val Pro
        105                 110                 115

GTG TGG AAA GAA GCA AAC ACC ACT CTA TTT TGT GCA TCA GAT     1075
Val Trp Lys Glu Ala Asn Thr Thr Leu Phe Cys Ala Ser Asp
                120                 125                 130

GCT AAA GCA TAT AAG ACA GAG GCA CAT AAT GTT TGG GCC ACA     1117
Ala Lys Ala Tyr Lys Thr Glu Ala His Asn Val Trp Ala Thr
            135                 140                 145

CAT GCC TGT GTA CCC ACA GAC CCC AAA CCA CAA GAA ATA AAA     1159
His Ala Cys Val Pro Thr Asp Pro Lys Pro Gln Glu Ile Lys
                150                 155

TTG GAA AAT GTG ACA GAA AAT TTT AAC ATG TGG AAA AAT AAC     1201
Leu Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn
160                 165                 170

ATG GTA GAA CAG ATG CAT GAG GAT ATA ATC AGT TTA TGG GAT     1243
Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp
    175                 180                 185

CAA AGC CTA AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT     1285
Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val
        190                 195                 200

ACT TTA AAT TGC ACT GAT TTG AGG AAT AAT ACT AAT ACC AAT     1327
Thr Leu Asn Cys Thr Asp Leu Arg Asn Asn Thr Asn Thr Asn
            205                 210                 215

AGT ACC TAC GGA AAA ATA ATG GAG GGA GGA GAG ATA AAA AAC     1369
Ser Thr Tyr Gly Lys Ile Met Glu Gly Gly Glu Ile Lys Asn
                220                 225

TGC TCT TTC AAT ATC ACC ACA AGC ATA AAA GAT AAG CTG AAA     1411
Cys Ser Phe Asn Ile Thr Thr Ser Ile Lys Asp Lys Leu Lys
230                 235                 240

GAT ATG TCA CTT TTT TAT AAA CTT GAT GTA GTA CCA ATA GGT     1453
Asp Met Ser Leu Phe Tyr Lys Leu Asp Val Val Pro Ile Gly
    245                 250                 255
```

```
AAT AAT AGT AAT ACT ACT AGT TAT AGG TTG ATA AGT TGT AAC     1495
Asn Asn Ser Asn Thr Thr Ser Tyr Arg Leu Ile Ser Cys Asn
        260                 265                 270

ACC TCA GTC ATT ACA CAA GCC TGT CCA AAG ACA TCC TTT GAG     1537
Thr Ser Val Ile Thr Gln Ala Cys Pro Lys Thr Ser Phe Glu
            275                 280                 285

CCA ATT CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT GCG ATT     1579
Pro Ile Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile
                290                 295

CTC AAG TGT AAT GAT AAT AAG TTC AAT GGA ACA GGA CCA TGT     1621
Leu Lys Cys Asn Asp Asn Lys Phe Asn Gly Thr Gly Pro Cys
300                 305                 310

CCA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AGG CCA     1663
Pro Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro
    315                 320                 325

GTA GTA TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA     1705
Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
        330                 335                 340

AAA GAG GTA GTC CTT AGA TCT GAA AAT TTC ACG GAC AAT GCT     1747
Lys Glu Val Val Leu Arg Ser Glu Asn Phe Thr Asp Asn Ala
            345                 350                 355

AAA ACC ATA ATA GTA CAG CTG AAC GAA TCT GTA ATA ATT GAT     1789
Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Ile Ile Asp
                360                 365

TGT ATG AGA CCC AAC AAC AAT ACA AGA ACA AGT ATA CCT ATG     1831
Cys Met Arg Pro Asn Asn Asn Thr Arg Thr Ser Ile Pro Met
370                 375                 380

GGA CCA GGG AAA GCA TTT TAT GCA ACA GGA GAT GTA ATA GGA     1873
Gly Pro Gly Lys Ala Phe Tyr Ala Thr Gly Asp Val Ile Gly
    385                 390                 395

GAT ATA AGA CGA GCA CAT TGT AAC ATT AGT AGA GCA GGA TGG     1915
Asp Ile Arg Arg Ala His Cys Asn Ile Ser Arg Ala Gly Trp
        400                 405                 410

AAT ACC ACT TTA CAA CAG ATA GCT AAA AAA TTA AGA GAA AAA     1957
Asn Thr Thr Leu Gln Gln Ile Ala Lys Lys Leu Arg Glu Lys
            415                 420                 425

TTT GAG AAC AAA ACA ATA GTT TTT AAT CAC TCC TCA GGA GGG     1999
Phe Glu Asn Lys Thr Ile Val Phe Asn His Ser Ser Gly Gly
            430                 435

GAC CCA GAA ATT GTA ATG CAC ACT TTT AAT TGT GGA GGG GAA     2041
Asp Pro Glu Ile Val Met His Thr Phe Asn Cys Gly Gly Glu
440                 445                 450

TTT TTC TGC TGT AAT TCA ACA CCA CTG TTT AAT AGT ACT TGG     2083
Phe Phe Cys Cys Asn Ser Thr Pro Leu Phe Asn Ser Thr Trp
    455                 460                 465

AAT GAT GCA CAA CTG TTT AAT AGT ACT TGG GAT GAT ACT AAA     2125
Asn Asp Ala Gln Leu Phe Asn Ser Thr Trp Asp Asp Thr Lys
        470                 475                 480
```

```
TGG TCA AAA GGC ACT AAC GAA AAT GAC ACA ATC ACC CTC CAT     2167
Trp Ser Lys Gly Thr Asn Glu Asn Asp Thr Ile Thr Leu His
            485                 490                 495

TGC AGA ATA AAA CAA ATT ATA AAT ATG TGG CAG GAA GTA GGA     2209
Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly
                500                 505

AAA GCA ATG TAT GCC CCT CCC ATC AAA GGA CAA ATT AGA TGT     2251
Lys Ala Met Tyr Ala Pro Pro Ile Lys Gly Gln Ile Arg Cys
510                 515                 520

GAA TCA AAT ATT ACA GGG CTG CTA TTA ACA AGA GAT GGT GGT     2293

Glu Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly
    525                 530                 535

AAC GAC ACG AGC AAG AAT AAC ACT GAG ATT TTC AGA CCT GGA     2335
Asn Asp Thr Ser Lys Asn Asn Thr Glu Ile Phe Arg Pro Gly
        540                 545                 550

GGA GGA AAT ATG AAG GAC AAT TGG AGA AGT GAA TTA TAT AAA     2377
Gly Gly Asn Met Lys Asp Asn Trp Arg Ser Glu Leu Tyr Lys
            555                 560                 565

TAT AAA GTA ATA AAA ATT GAA CCA TTA GGA GTA GCA CCC ATC     2419
Tyr Lys Val Ile Lys Ile Glu Pro Leu Gly Val Ala Pro Ile
                570                 575             579

TAGGCAAAGA GAAGAGTGGT GCAGAGAGAA AAAAGAGCAG TGACACTAGG     2469

AGCTATGTTC CTTGGGTTCT TGGGAGCAGC AGGAAGCACT ATGGGCGATA     2519

AGCTTTAATG CGGTAGTTTA TCACAGTTAA ATTCGTAACG CAGTCAGGCA     2569

CCGTGTATGA AATCTAACAA TGCGACCTGC AGAAGCTTAG AACCGAGGAA     2619

CTTGTTTATT GCAGCTTATA ATGGTTACAA ATAAAGCAAT AGCATCACAA     2669

ATTTCACAAA TAAAGCATTT TTTTCACTGC ATTCTAGTTG TGGTTTGTCC     2719

AAACTCATCA ATGTATCTTA TCATGTCTGG ATCGGGAATT AATTCGGCGC     2769

AGCACCATGG CCTGAAATAA CCTCTGAAAG A                         2800
```

(2) INFORMATION FOR SEQ ID NO:31

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 579 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Ser Val Ser Ser Cys Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Cys
 1               5                  10                  15

Ser Glu Tyr Cys Leu Ser His Leu Val Asn Leu Arg Glu Asp Trp Gly
            20                  25                  30

Pro Cys Asp Lys Leu Gln Arg Glu Arg Pro Thr Thr Pro Ile Ile Ser
        35                  40                  45
```

```
Tyr Pro  *  Gly Leu Phe Cys Val Val Arg Ser Gly Met Gly Gly Thr
     50                 55                  60

Ala Ala Arg Leu Gly Ala Val Ile Leu Phe Val Val Ile Val Gly Leu
 65                 70                  75                  80

His Gly Val Arg Gly Lys Tyr Ala Leu Ala Asp Ala Ser Leu Lys Met
                85                  90                  95

Ala Asp Pro Asn Arg Phe Arg Gly Lys Asp Leu Pro Val Leu Asp Gln
            100                 105                 110

Leu Leu Glu Val Pro Val Trp Lys Glu Ala Asn Thr Thr Leu Phe Cys
        115                 120                 125

Ala Ser Asp Ala Lys Ala Tyr Lys Thr Glu Ala His Asn Val Trp Ala
    130                 135                 140

Thr His Ala Cys Val Pro Thr Asp Pro Lys Pro Gln Glu Ile Lys Leu
145                 150                 155                 160

Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu
                165                 170                 175

Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro
            180                 185                 190

Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys Thr Asp Leu
        195                 200                 205

Arg Asn Asn Thr Asn Thr Asn Ser Thr Tyr Gly Lys Ile Met Glu Gly
    210                 215                 220

Gly Glu Ile Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Lys Asp
225                 230                 235                 240

Lys Leu Lys Asp Met Ser Leu Phe Tyr Lys Leu Asp Val Val Pro Ile
                245                 250                 255

Gly Asn Asn Ser Asn Thr Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr
            260                 265                 270

Ser Val Ile Thr Gln Ala Cys Pro Lys Thr Ser Phe Glu Pro Ile Pro
        275                 280                 285

Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp
    290                 295                 300

Asn Lys Phe Asn Gly Thr Gly Pro Cys Pro Asn Val Ser Thr Val Gln
305                 310                 315                 320

Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn
                325                 330                 335

Gly Ser Leu Ala Glu Lys Glu Val Val Leu Arg Ser Glu Asn Phe Thr
            340                 345                 350

Asp Asn Ala Lys Thr Ile Ile Val Gln Leu Asn Glu Ser Val Ile Ile
        355                 360                 365

Asp Cys Met Arg Pro Asn Asn Asn Thr Arg Thr Ser Ile Pro Met Gly
    370                 375                 380

Pro Gly Lys Ala Phe Tyr Ala Thr Gly Asp Val Ile Gly Asp Ile Arg
385                 390                 395                 400
```

```
Arg Ala His Cys Asn Ile Ser Arg Ala Gly Trp Asn Thr Thr Leu Gln
                405                 410                 415

Gln Ile Ala Lys Lys Leu Arg Glu Lys Phe Glu Asn Lys Thr Ile Val
            420                 425                 430

Phe Asn His Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Thr Phe
        435                 440                 445

Asn Cys Gly Gly Glu Phe Phe Cys Cys Asn Ser Thr Pro Leu Phe Asn
    450                 455                 460

Ser Thr Trp Asn Asp Ala Gln Leu Phe Asn Ser Thr Trp Asp Asp Thr
465                 470                 475                 480

Lys Trp Ser Lys Gly Thr Asn Glu Asn Asp Thr Ile Thr Leu His Cys
                485                 490                 495

Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met
            500                 505                 510

Tyr Ala Pro Pro Ile Lys Gly Gln Ile Arg Cys Glu Ser Asn Ile Thr
        515                 520                 525

Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn Asp Thr Ser Lys Asn Asn
    530                 535                 540

Thr Glu Ile Phe Arg Pro Gly Gly Gly Asn Met Lys Asp Asn Trp Arg
545                 550                 555                 560

Ser Glu Leu Tyr Lys Tyr Lys Val Ile Lys Ile Glu Pro Leu Gly Val
                565                 570                 575

Ala Pro Ile
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1533 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
ATGGGGGGGA CTGCCGCCAG GTTGGGGGCC GTGATTTTGT TTGTCGTCAT    50

AGTGGGCCTC CATGGGGTCC GCGGCAAATA TGCCTTGGCG GATGCCTCTC    100

TCAAGATGGC CGACCCCAAT CGATTTCGCG GCAAAGACCT TCCGGTCCTG    150

GACCAGCTGC TCGAG GTA CCT GTG TGG AAA GAA GCA ACC ACC      192
               Val Pro Val Trp Lys Glu Ala Thr Thr
                1               5

ACT CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG   234
Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu
 10                  15                  20

GTA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC   276
Val His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp
     25                  30                  35
```

```
CCC AAC CCA CAA GAA ATA GGA TTG GAA AAT GTA ACA GAA AAT      318
Pro Asn Pro Gln Glu Ile Gly Leu Glu Asn Val Thr Glu Asn
        40                  45                  50

TTT AAC ATG TGG AAA AAT AAC ATG GTA GAA CAG ATG CAT GAG      360
Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His Glu
    55                  60                  65

GAT ATA ATC AGT TTA TGG GAT CAA AGC TTA AAG CCA TGT GTA      402
Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro Cys Val
                70                  75

AAA TTA ACC CCA CTA TGT GTT ACT TTA AAT TGC ACT GAT TTG      444
Lys Leu Thr Pro  Leu Cys Val Thr Leu Asn Cys Thr Asp Leu
 80                  85                  90

AAA AAT GCT ACT AAT ACC ACT AGT AGC AGC TGG GGA AAG ATG      486
Lys Asn Ala Thr Asn Thr Thr Ser Ser Ser Trp Gly Lys Met
     95                  100                 105

GAG AGA GGA GAA ATA AAA AAC TGC TCT TTC AAT GTC ACC ACA      528
Glu Arg Gly Glu Ile Lys Asn Cys Ser Phe Asn Val Thr Thr
        110                 115                 120

AGT ATA AGA GAT AAG ATG AAG AAT GAA TAT GCA CTT TTT TAT      570
Ser Ile Arg Asp Lys Met Lys Asn Glu Tyr Ala Leu Phe Tyr
    125                 130                 135

AAA CTT GAT GTA GTA CCA ATA GAT AAT GAT AAT ACT AGC TAT      612
Lys Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr Ser Tyr
            140                 145

AGG TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCC TGT      654
Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys
150                 155                 160

CCA AAG GTG TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT GCC      696
Pro Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
    165                 170                 175

CCG GCT GGT TTT GCG ATT CTA AAG TGT AGA GAT AAA AAG TTC      738
Pro Ala Gly Phe Ala Ile Leu Lys Cys Arg Asp Lys Lys Phe
        180                 185                 190

AAC GGA ACA GGA CCA TGT ACA AAT GTC AGC ACA GTA CAA TGT      780
Asn Gly Thr Gly Pro Cys Thr Asn Val Ser Thr Val Gln Cys
    195                 200                 205

ACA CAT GGA ATT AGG CCA GTA GTA TCA ACT CAA CTG CTG TTA      822
Thr His Gly Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu
            210                 215

AAT GGC AGT TTA GCA GAA GAA GAA GTA GTA ATT AGA TCT GCC      864
Asn Gly Ser Leu Ala Glu Glu Glu Val Val Ile Arg Ser Ala
220                 225                 230

AAT TTC TCG GAC AAT GCT AAA ACC ATA ATA GTA CAG CTG AAC      906
Asn Phe Ser Asp Asn Ala Lys Thr Ile Ile Val Gln Leu Asn
    235                 240                 245
```

```
GAA TCT GTA GAA ATT AAT TGT ACA AGA CCC AAC AAC AAT ACA      948
Glu Ser Val Glu Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr
        250                 255                 260

AGA AGA AGT ATA CAT ATA GGA CCA GGG AGA GCA TTT TAT GCA      990
Arg Arg Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Ala
            265                 270                 275

ACA GGA GAA ATA ATA GGA GAC ATA AGA CAA GCA CAT TGT AAC     1032
Thr Gly Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn
                280                 285

CTT AGT AGC ACA AAA TGG AAT AAT ACT TTA AAA CAG ATA GTT     1074
Leu Ser Ser Thr Lys Trp Asn Asn Thr Leu Lys Gln Ile Val
290                 295                 300

ACA AAA TTA AGA GAA CAT TTT AAT AAA ACA ATA GTC TTT AAT     1116
Thr Lys Leu Arg Glu His Phe Asn Lys Thr Ile Val Phe Asn
    305                 310                 315

CAC TCC TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT     1158
His Ser Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe
        320                 325                 330

AAT TGT GGA GGG GAA TTT TTC TAC TGT AAT ACA ACA CCA CTG     1200
Asn Cys Gly Gly Glu Phe Phe Tyr Cys Asn Thr Thr Pro Leu
            335                 340                 345

TTT AAT AGT ACT TGG AAT TAT ACT TAT ACT TGG AAT AAT ACT     1242
Phe Asn Ser Thr Trp Asn Tyr Thr Tyr Thr Trp Asn Asn Thr
                350                 355

GAA GGG TCA AAT GAC ACT GGA AGA AAT ATC ACA CTC CAA TGC     1284
Glu Gly Ser Asn Asp Thr Gly Arg Asn Ile Thr Leu Gln Cys
360                 365                 370

AGA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA     1326
Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
    375                 380                 385

GCA ATG TAT GCC CCT CCC ATA AGA GGA CAA ATT AGA TGC TCA     1368

Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile Arg Cys Ser
        390                 395                 400

TCA AAT ATT ACA GGG CTG CTA TTA ACA AGA GAT GGT GGT AAT     1410
Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn
            405                 410                 415

AAC AGC GAA ACC GAG ATC TTC AGA CCT GGA GGA GGA GAT ATG     1452
Asn Ser Glu Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met
                420                 425

AGG GAC AAT TGG AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA     1494
Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val
430                 435                 440

AAA ATT GAA CCA TTA GGA GTA GCA CCC ACC AAG GCA TAA        1533
Lys Ile Glu Pro Leu Gly Val Ala Pro Thr Lys Ala  *
    445                 450                 455
```

(2) INFORMATION FOR SEQ ID NO:33:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 456 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu Phe Cys Ala Ser Asp
1 5 10 15

Ala Lys Ala Tyr Asp Thr Glu Val His Asn Val Trp Ala Thr His Ala
20 25 30

Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Ile Gly Leu Glu Asn Val
35 40 45

Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met Val Glu Gln Met His
50 55 60

Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu Lys Pro Cys Val Lys
65 70 75 80

Leu Thr Pro Leu Cys Val Thr Leu Asn Cys Thr Asp Leu Lys Asn Ala
85 90 95

Thr Asn Thr Thr Ser Ser Ser Trp Gly Lys Met Glu Arg Gly Glu Ile
100 105 110

Lys Asn Cys Ser Phe Asn Val Thr Thr Ser Ile Arg Asp Lys Met Lys
115 120 125

Asn Glu Tyr Ala Leu Phe Tyr Lys Leu Asp Val Val Pro Ile Asp Asn
130 135 140

Asp Asn Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr
145 150 155 160

Gln Ala Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
165 170 175

Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Arg Asp Lys Lys Phe Asn
180 185 190

Gly Thr Gly Pro Cys Thr Asn Val Ser Thr Val Gln Cys Thr His Gly
195 200 205

Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
210 215 220

Glu Glu Glu Val Val Ile Arg Ser Ala Asn Phe Ser Asp Asn Ala Lys
225 230 235 240

Thr Ile Ile Val Gln Leu Asn Glu Ser Val Glu Ile Asn Cys Thr Arg
245 250 255

Pro Asn Asn Asn Thr Arg Arg Ser Ile His Ile Gly Pro Gly Arg Ala
260 265 270

Phe Tyr Ala Thr Gly Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys
275 280 285

Asn Leu Ser Ser Thr Lys Trp Asn Asn Thr Leu Lys Gln Ile Val Thr
290 295 300

```
Lys Leu Arg Glu His Phe Asn Lys Thr Ile Val Phe Asn His Ser Ser
305                 310                 315                 320

Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gly Gly Glu
                325                 330                 335

Phe Phe Tyr Cys Asn Thr Thr Pro Leu Phe Asn Ser Thr Trp Asn Tyr
            340                 345                 350

Thr Tyr Thr Trp Asn Asn Thr Glu Gly Ser Asn Asp Thr Gly Arg Asn
        355                 360                 365

Ile Thr Leu Gln Cys Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu
    370                 375                 380

Val Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile Arg Cys
385                 390                 395                 400

Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn Asn
                405                 410                 415

Ser Glu Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn
            420                 425                 430

Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu
        435                 440                 445

Gly Val Ala Pro Thr Lys Ala *
    450                 455
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GGGAATTCGG ATCCAGAGCA GAAGACAGTG GCAATGA 37

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CTCGAGCTCC TGAAGACAGT CAGACTCATC AAG 33

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GGTCTAGAAG CTTTAGCCCA TAGTGCTTCC TGCTGCTCC 39

(2) INFORMATION FOR SEQ ID NO:37:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GGGCGGATCC TCGAGGTACC TGTRTGGAAA GAAGCA 36

(2) INFORMATION FOR SEQ ID NO:38:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GGTCTAGAAG CTTTATGCTC CYAAGAACCC AAGGAACA 38

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: Amino Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Ile Gly Pro Gly Arg Ala Phe
1 5

(2) INFORMATION FOR SEQ ID NO:40:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: Amino Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Ile Gly Pro Gly Arg Ala Trp
1 5

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: Amino Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Leu Gly Pro Gly Ser Thr Phe
1 5

(2) INFORMATION FOR SEQ ID NO:42:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: Amino Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Ile Gly Pro Gly Arg Val Leu
1 5

(2) INFORMATION FOR SEQ ID NO:43:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: Amino Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Ile Gly Pro Gly Ser Ala Phe
1 5

(2) INFORMATION FOR SEQ ID NO:44:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: Amino Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Ile Gly Pro Gly Arg
1 5

WHAT IS CLAIMED IS:

1. An isolated polypeptide comprising an HIV gp120 amino acid sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof.

2. The polypeptide of Claim 1 wherein the polypeptide additionally comprises a flag epitope sequence.

3. The polypeptide of Claim 2 wherein the flag epitope sequence is HSV gD-1 flag epitope sequence.

4. The polypeptide of Claim 2 wherein the flag epitope sequence is fused to the HIV gp120 amino acid sequence.

5. An oligonucleotide of not more than five kilobases encoding an HIV gp120 polypeptide sequence comprising an amino acid sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof.

6. The oligonucleotide of Claim 5 wherein the oligonucleotide includes a nucleotide sequence selected from the group consisting of Sequence ID Nos. 1, 3, 5, 7, 9, 11, 13, 15, 7, 19, 21, 23, 25, and 27, and fragments thereof.

7. The oligonucleotide of Claim 5 wherein the amino acid sequence encoded by the oligonucleotide additionally comprises a flag epitope.

8. The oligonucleotide of Claim 5 wherein the flag epitope is HSV gD-1 flag epitope.

9. The oligonucleotide of Claim 7 wherein the flag epitope is fused to the HIV gp120 amino acid sequence.

10. A vaccine comprising gp120 MN and an HIV gp120 polypeptide sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof in a suitable carrier.

11. A vaccine comprising:

a. a first gp120 polypeptide sequence or a fragment thereof; and

b. a breakthrough isolate HIV gp120 polypeptide sequence or a fragment thereof from a vaccinee vaccinated with said first HIV gp120 polypeptide sequence;

wherein said HIV gp120 polypeptide sequences are in a suitable carrier.

12. The vaccine of Claim 11 wherein said first HIV gp120 polypeptide sequence comprises gp120 MN, gp120 A244, gp120 MN-GNE6 (Sequence ID No. 31), or gp120 MN-GNE8 (Sequence ID No. 33).

13. The vaccine of Claim 12 wherein said vaccine additionally comprises a second gp120 polypeptide sequence comprising gp120 MN, gp120 A244, gp120 MN-GNE6 (Sequence ID No. 31), or gp120 MN-GNE8 (Sequence ID No. 33), or a fragment thereof, wherein said second HIV gp120 polypeptide sequence is different from said first HIV gp120 polypeptide sequence.

14. The vaccine of Claim 13 wherein said first gp120 polypeptide sequence comprises gp120 MN and said second gp120 polypeptide sequence comprises gp120 A244.

15. The vaccine of Claim 14 wherein said breakthrough isolate comprises an HIV gp120 polypeptide sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof in a suitable carrier.

16. The vaccine of Claim 13 wherein said first gp120 polypeptide sequence comprises gp120 MN and said second gp120 polypeptide sequence comprises gp120 MN-GNE8 (Sequence ID No. 33).

17. The vaccine of Claim 16 wherein said breakthrough isolate HIV gp120 polypeptide sequence is an HIV gp120 polypeptide sequence selected from the group consisting of Sequence ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28, and fragments thereof, in a suitable carrier.

18. The vaccine of Claim 13 wherein said breakthrough isolate HIV gp120 polypeptide is from a vaccinee vaccinated with said first and second HIV gp120 polypeptide sequences.

19. A method for making an HIV vaccine comprising adding an HIV gp120 polypeptide sequence or fragments thereof from a breakthrough isolate from a vaccinee to the vaccine with which the vaccinee was vaccinated.

20. The vaccine of Claim 11 wherein said first gp120 polypeptide sequence is from a macrophage-tropic HIV-1 strain.

21. The vaccine of Claim 11 wherein said first gp120 polypeptide sequence is from a T-cell-tropic HIV-1 strain.

22. The vaccine of Claim 21 wherein said vaccine additionally comprises a second gp120 polypeptide sequence or a fragment, from a macrophage-tropic HIV-1 strain.

23. The vaccine of Claim 22 wherein said first and second gp120 polypeptide sequences bind to different chemokine receptors.

24. The vaccine of Claim 23 wherein said first gp120 polypeptide sequence binds to CC-CKR-5 and said second gp 120 polypeptide sequence binds to CXC-CKR-4.

25. The vaccine of Claim 11 wherein said vaccine additionally comprises an virus engineered to induce a cytotoxic T-cell response.

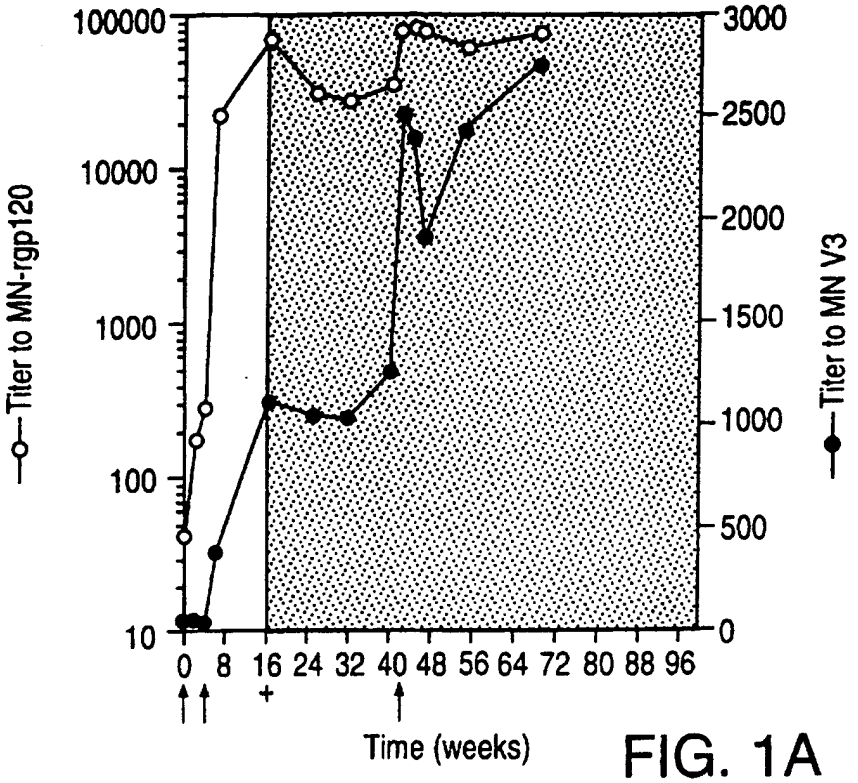
100000
10000
1000
100
10
3000
2500
2000
1500
1000
500
0
Titer to MN-rgp120
Titer to MN V3
0 8 16 24 32 40 48 56 64 72 80 88 96
+
Time (weeks)

FIG. 1A

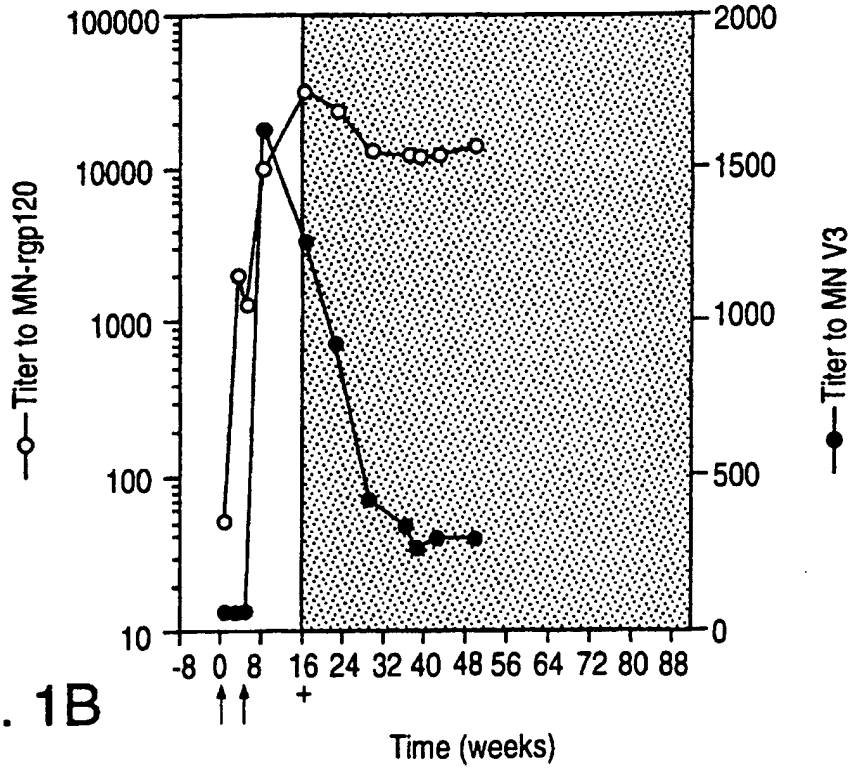
100000
10000
1000
100
10
2000
1500
1000
500
0
Titer to MN-rgp120
Titer to MN V3
-8 0 8 16 24 32 40 48 56 64 72 80 88
+
Time (weeks)

FIG. 1B

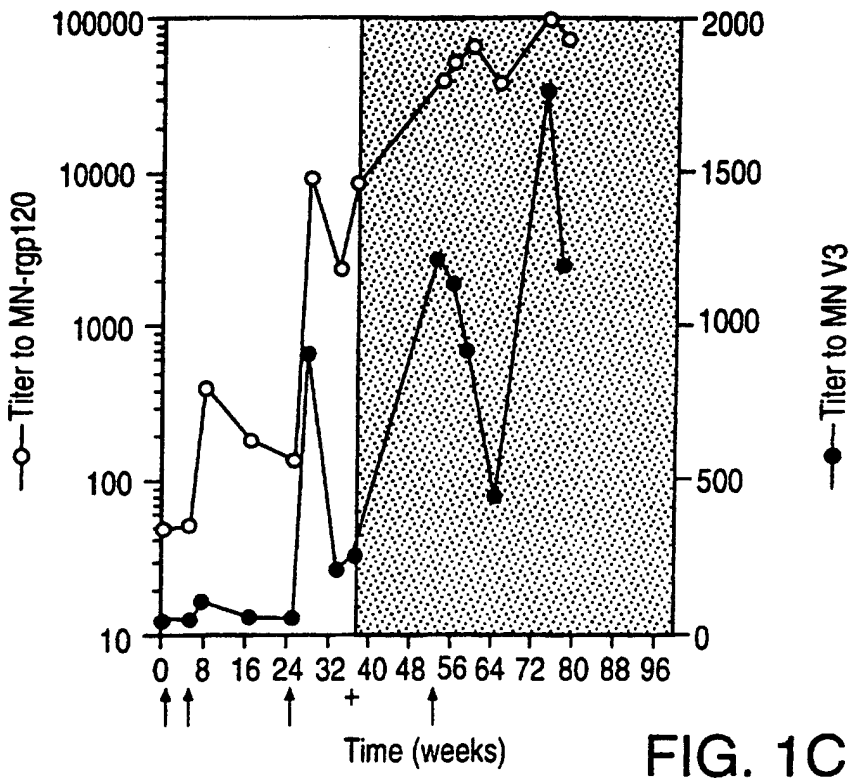
100000
10000
1000
100
10
2000
1500
1000
500
0
Titer to MN-rgp120
Titer to MN V3
0 8 16 24 32 40 48 56 64 72 80 88 96
Time (weeks)

FIG. 1C

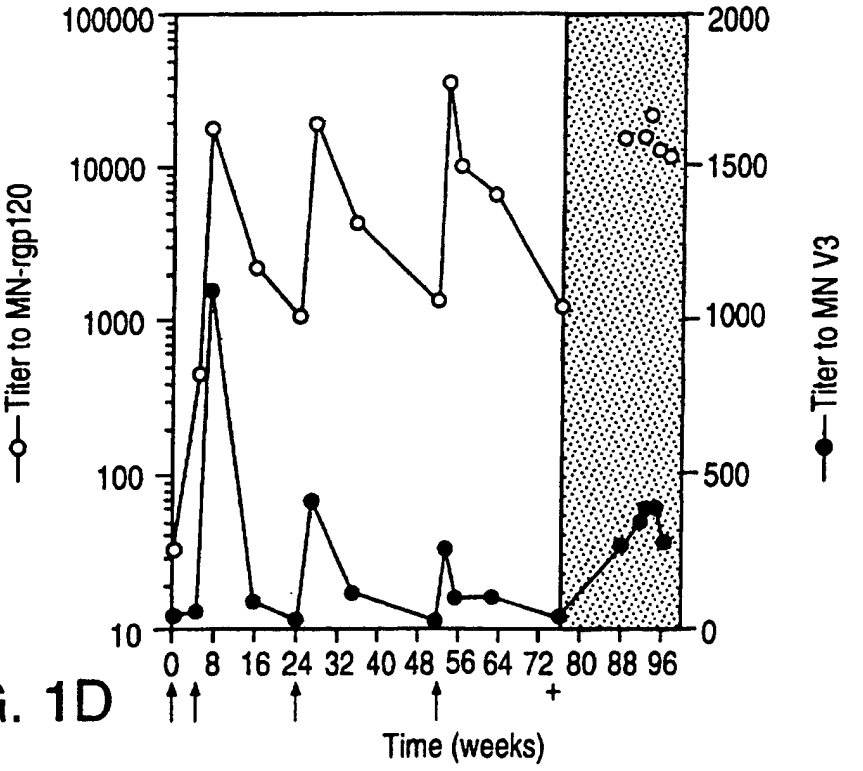
100000
10000
1000
100
10
2000
1500
1000
500
0
Titer to MN-rgp120
Titer to MN V3
0 8 16 24 32 40 48 56 64 72 80 88 96
Time (weeks)

FIG. 1D

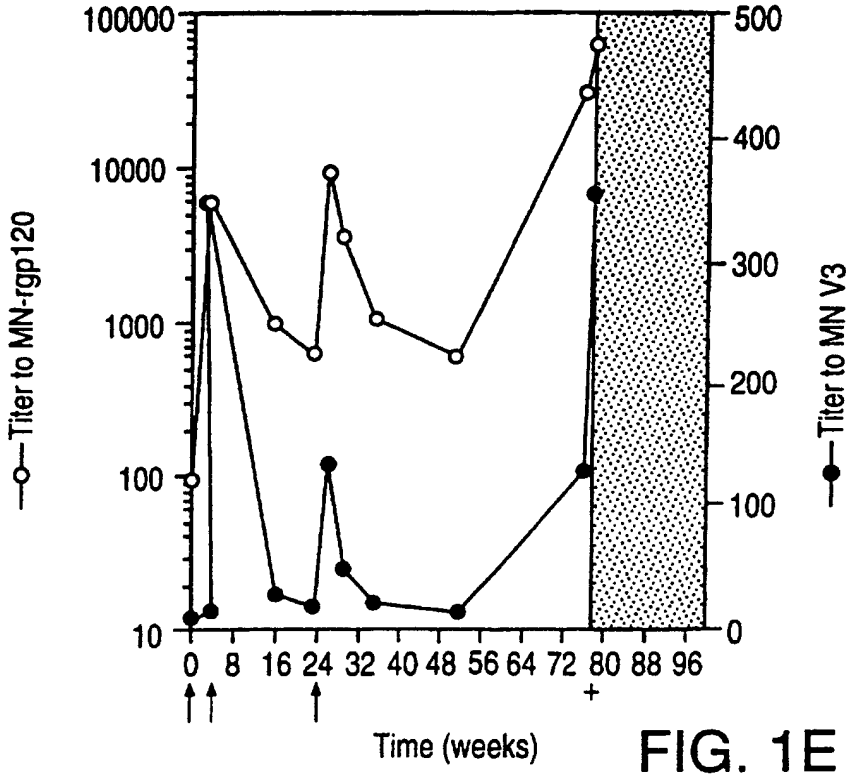
100000
10000
1000
100
10
Titer to MN-rgp120
500
400
300
200
100
0
Titer to MN V3
0 8 16 24 32 40 48 56 64 72 80 88 96
+
Time (weeks)

FIG. 1E

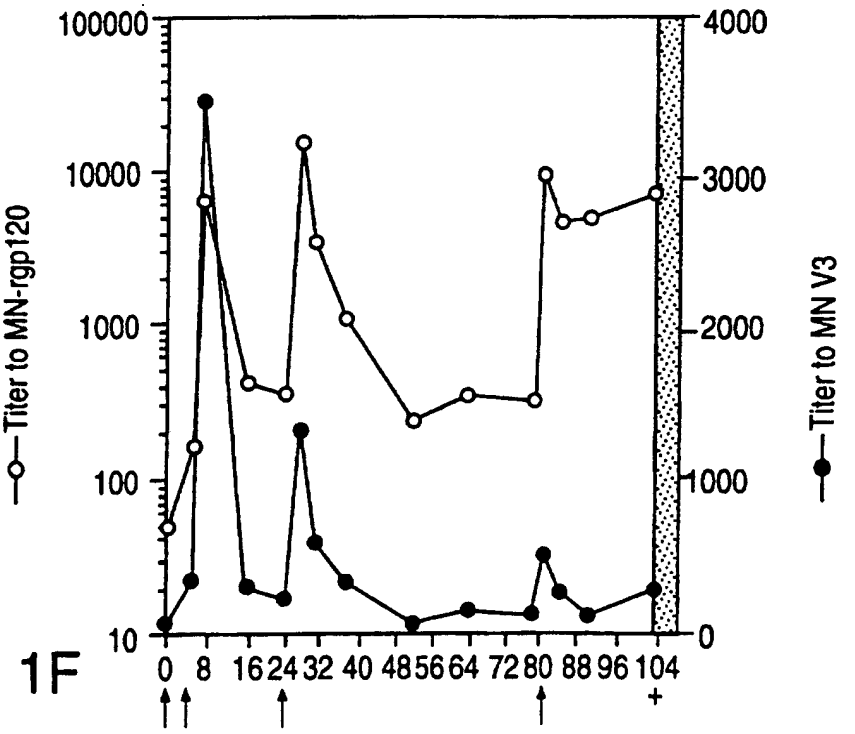
100000
10000
1000
100
10
Titer to MN-rgp120
4000
3000
2000
1000
0
Titer to MN V3
0 8 16 24 32 40 48 56 64 72 80 88 96 104
+
Time (weeks)

FIG. 1F

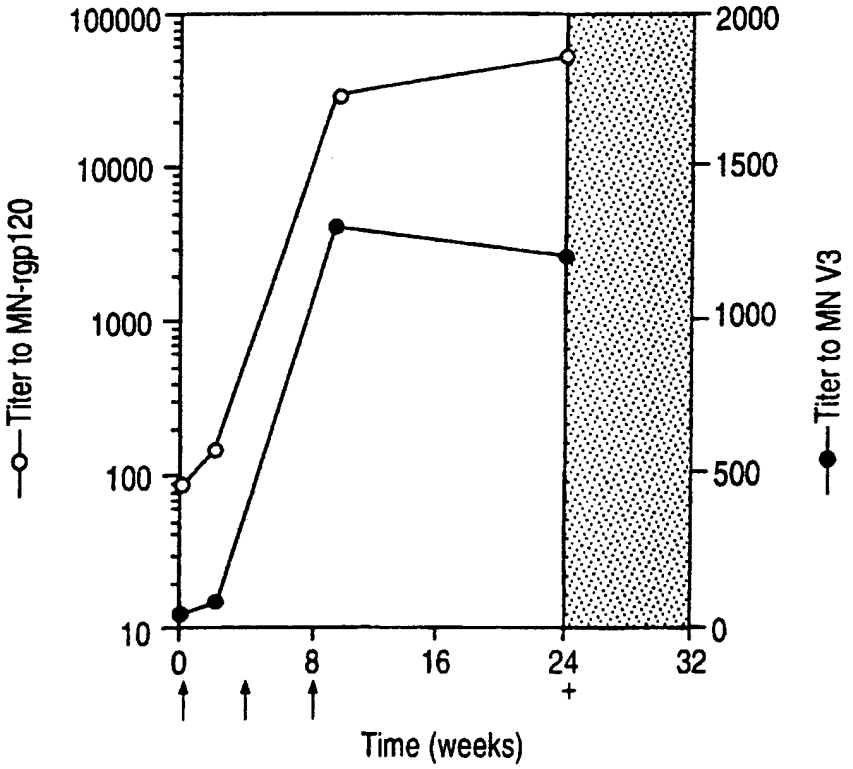
100000
10000
1000
100
10
2000
1500
1000
500
0
Titer to MN-rgp120
Titer to MN V3
0
8
16
24
32
+
Time (weeks)

FIG. 1G

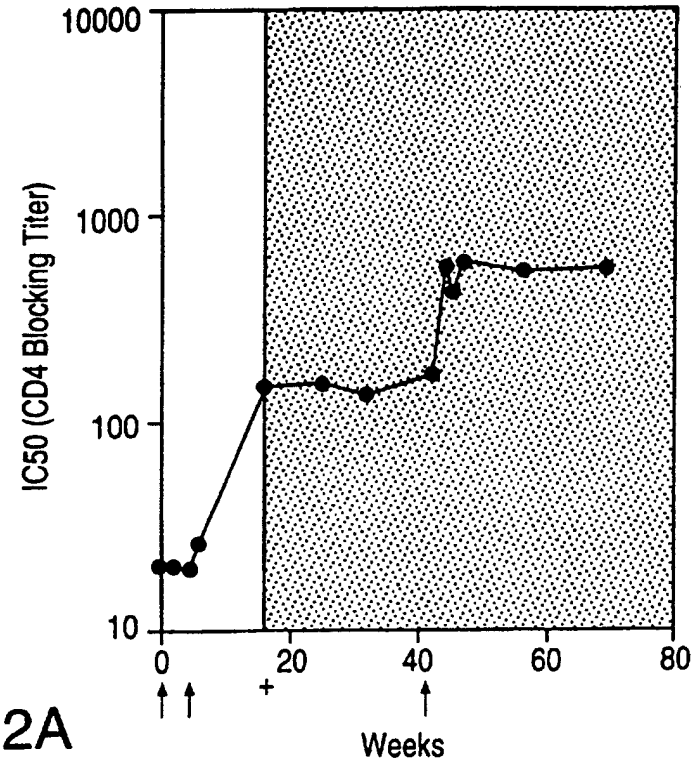
10000
1000
100
10
IC50 (CD4 Blocking Titer)
0
20
40
60
80
+
Weeks

FIG. 2A

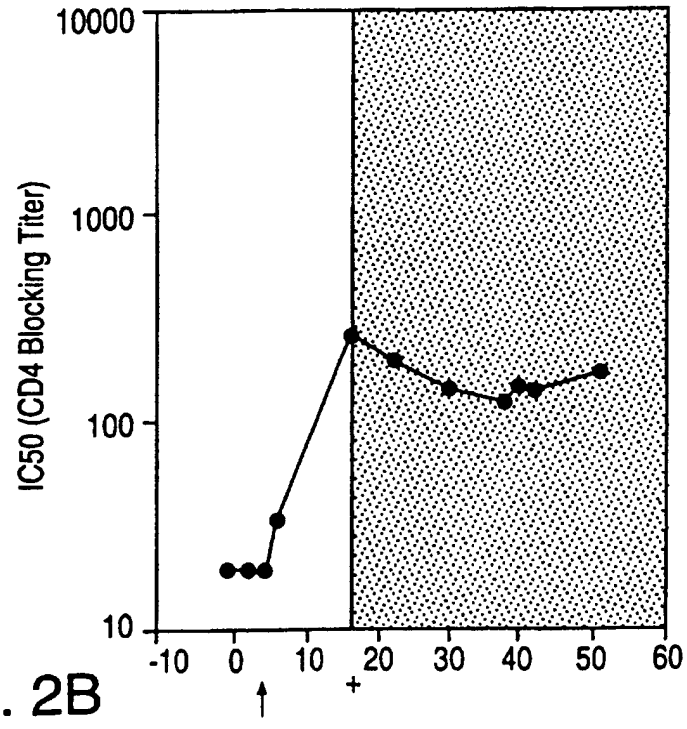
10000
1000
100
10
IC50 (CD4 Blocking Titer)
-10
0
10
20
30
40
50
60
+
Weeks

FIG. 2B

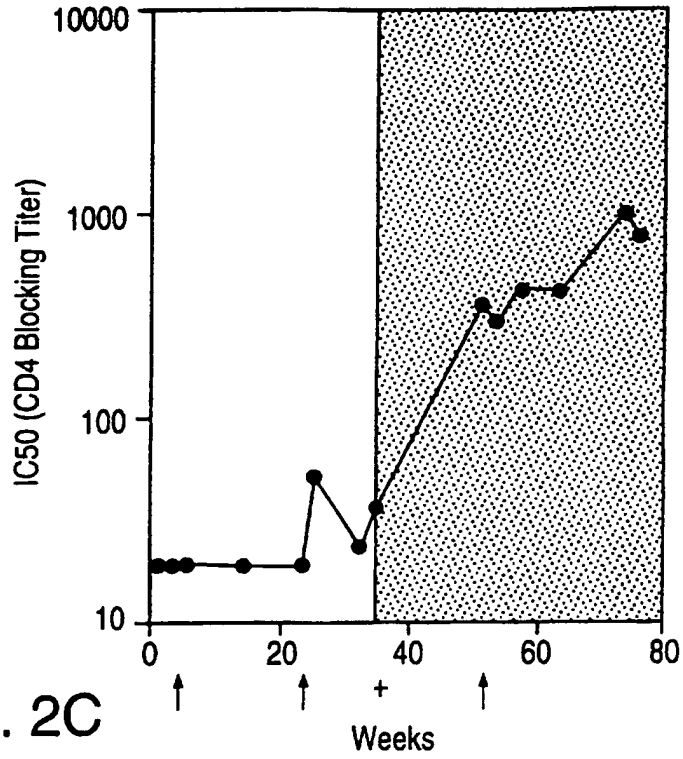
10000
1000
100
10
IC50 (CD4 Blocking Titer)
0
20
40
60
80
+
Weeks

FIG. 2C

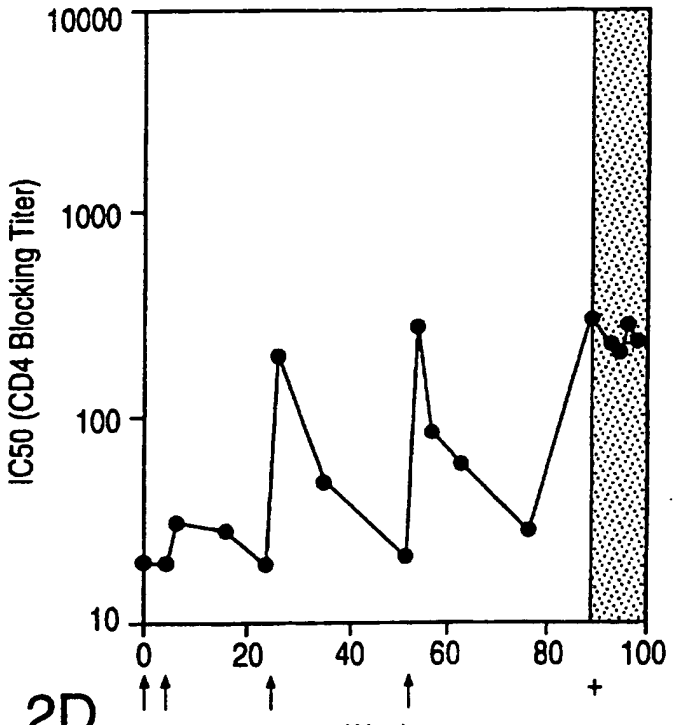
10000
1000
100
10
IC50 (CD4 Blocking Titer)
0
20
40
60
80
100
+
Weeks

FIG. 2D

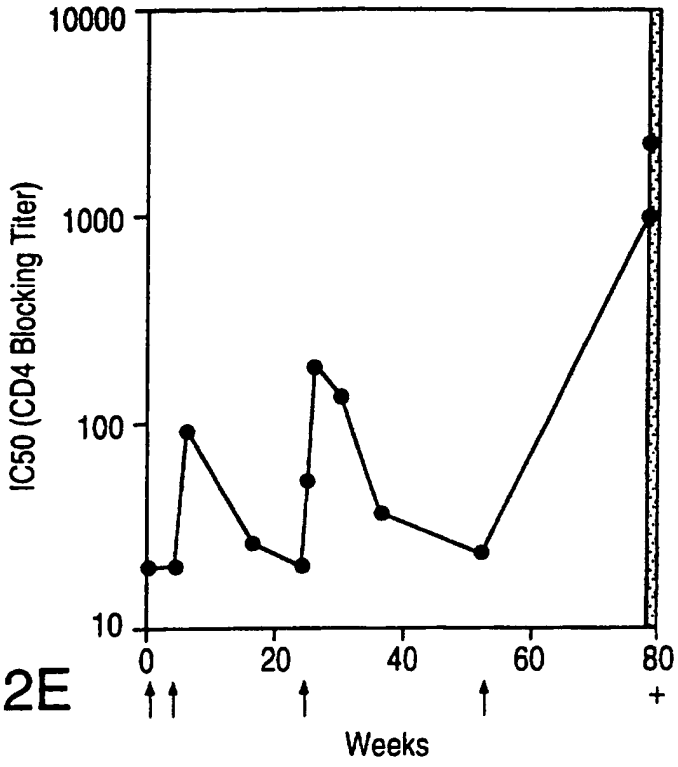
10000
1000
100
10
IC50 (CD4 Blocking Titer)
0
20
40
60
80
+
Weeks

FIG. 2E

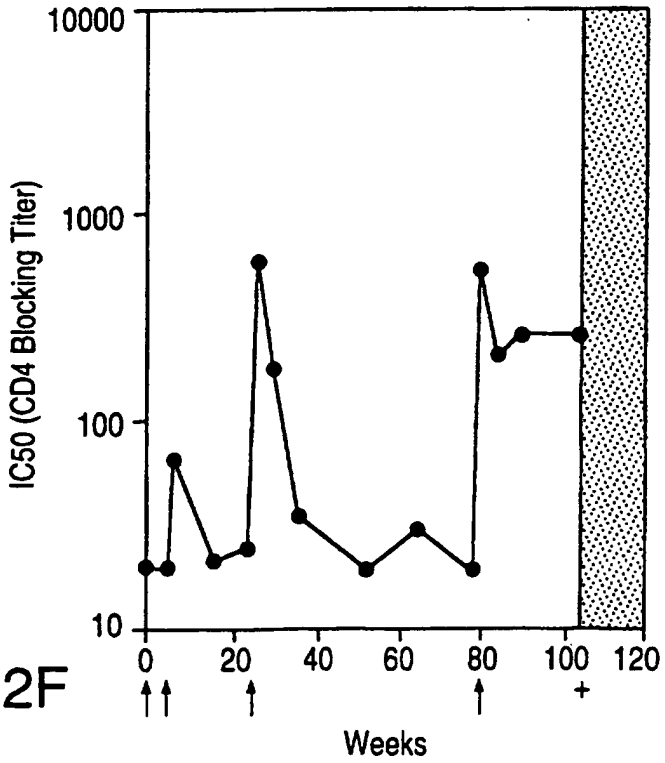
10000
1000
100
10
IC50 (CD4 Blocking Titer)
0
20
40
60
80
100
120
+
Weeks

FIG. 2F

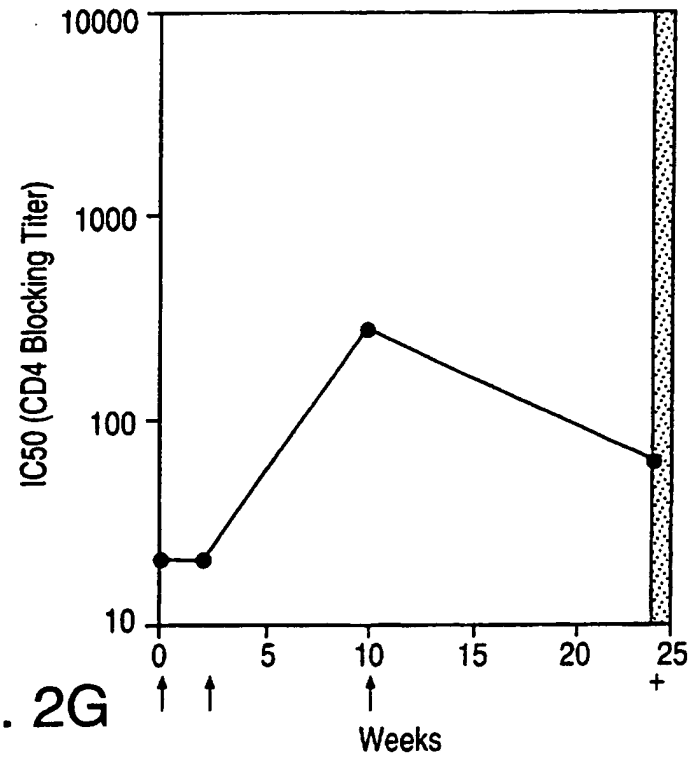

FIG. 2G

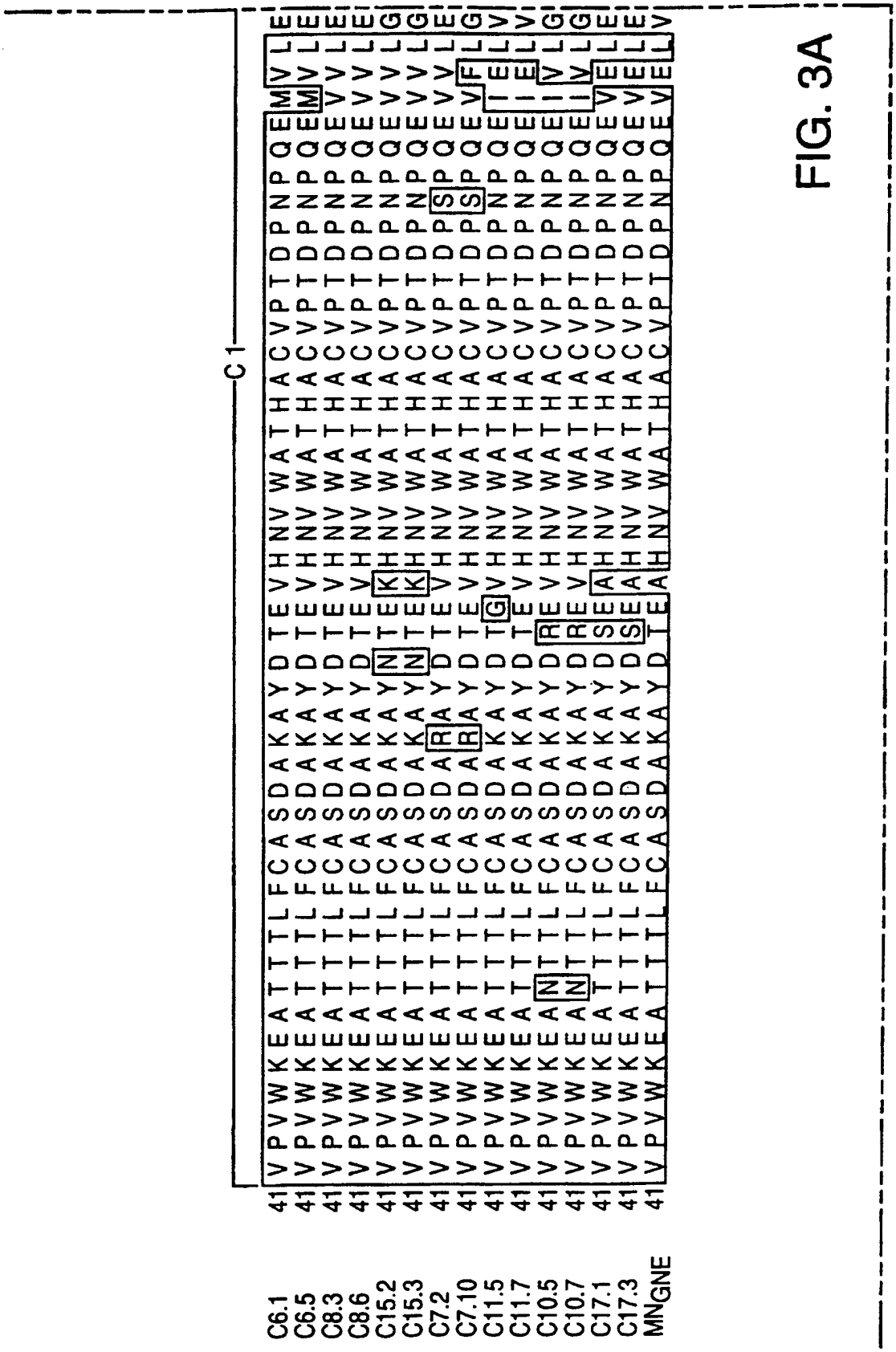
C1
41
C6.1
C6.5
C8.3
C8.6
C15.2
C15.3
C7.2
C7.10
C11.5
C11.7
C10.5
C10.7
C17.1
C17.3
MNGNE

FIG. 3A

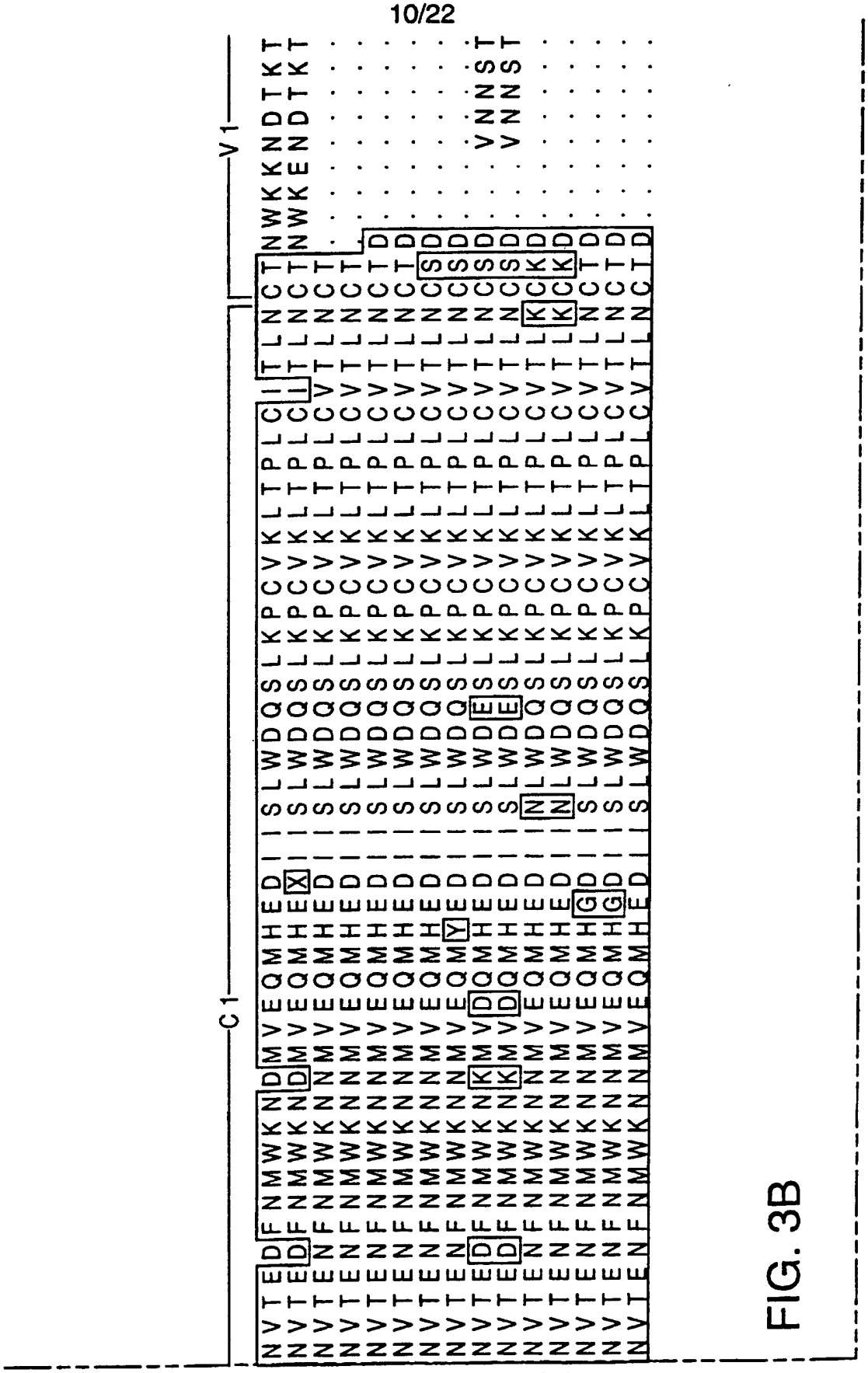

FIG. 3B

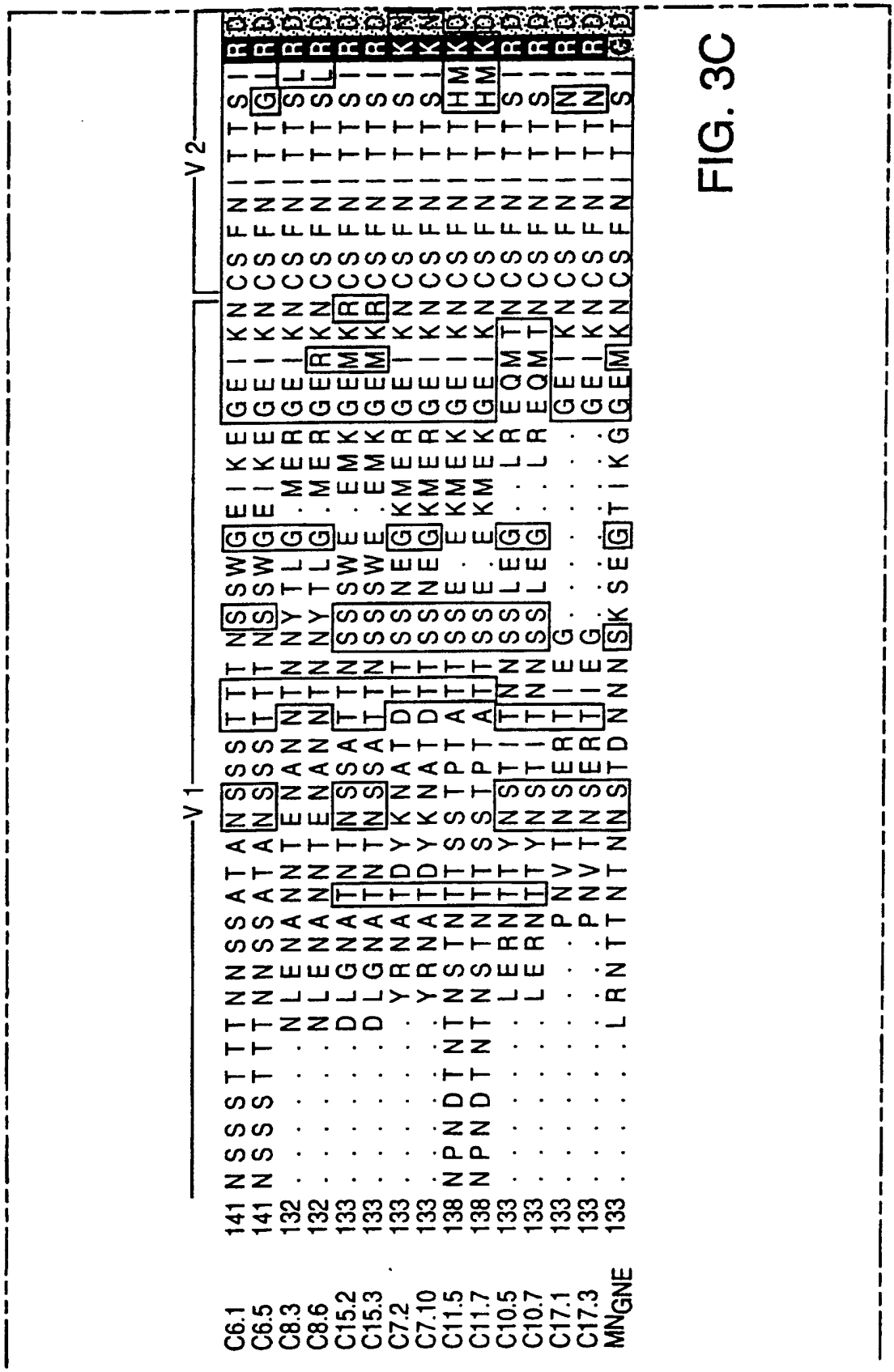
V1
V2
C6.1
C6.5
C8.3
C8.6
C15.2
C15.3
C7.2
C7.10
C11.5
C11.7
C10.5
C10.7
C17.1
C17.3
MNGNE

FIG. 3C

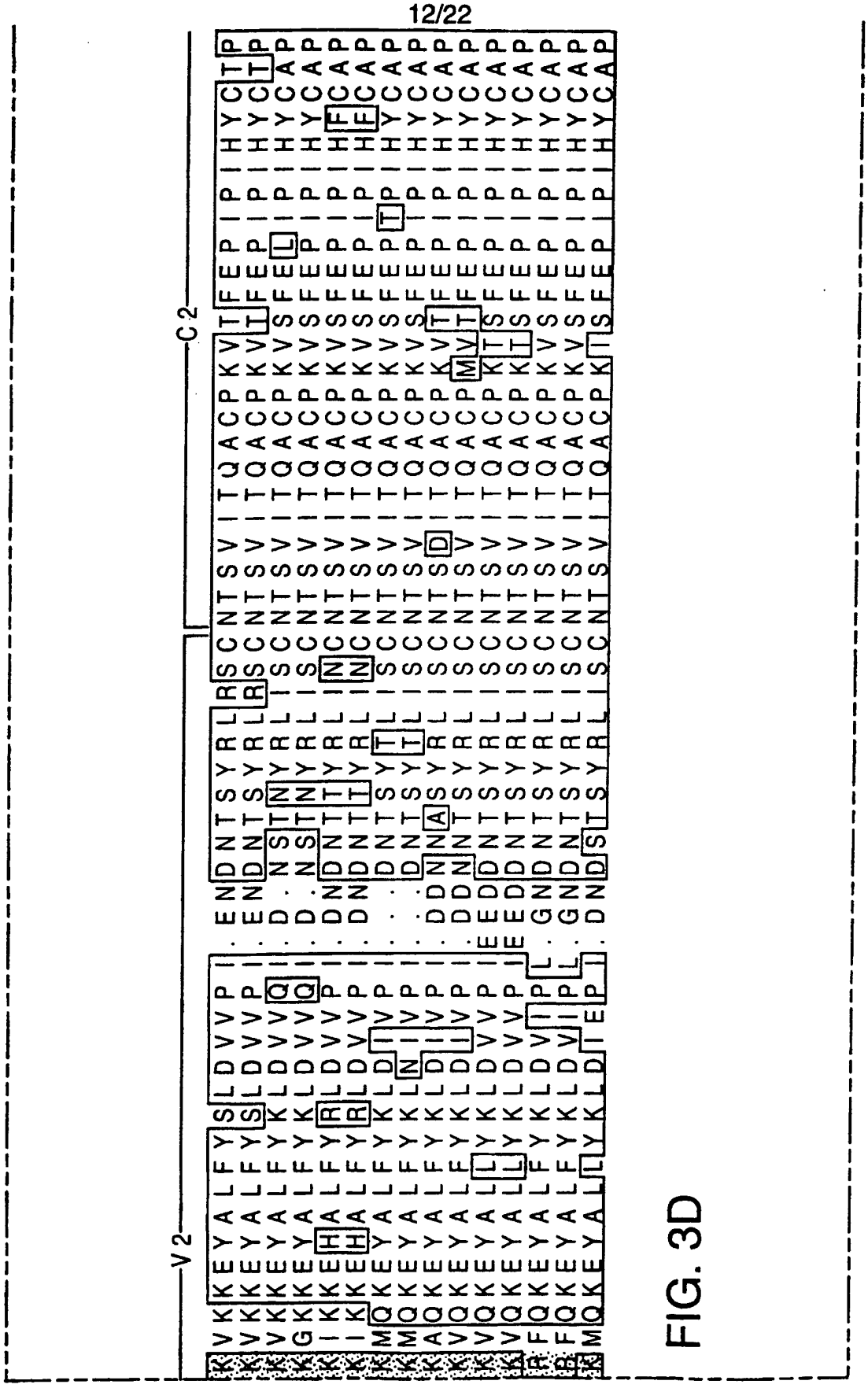

FIG. 3D

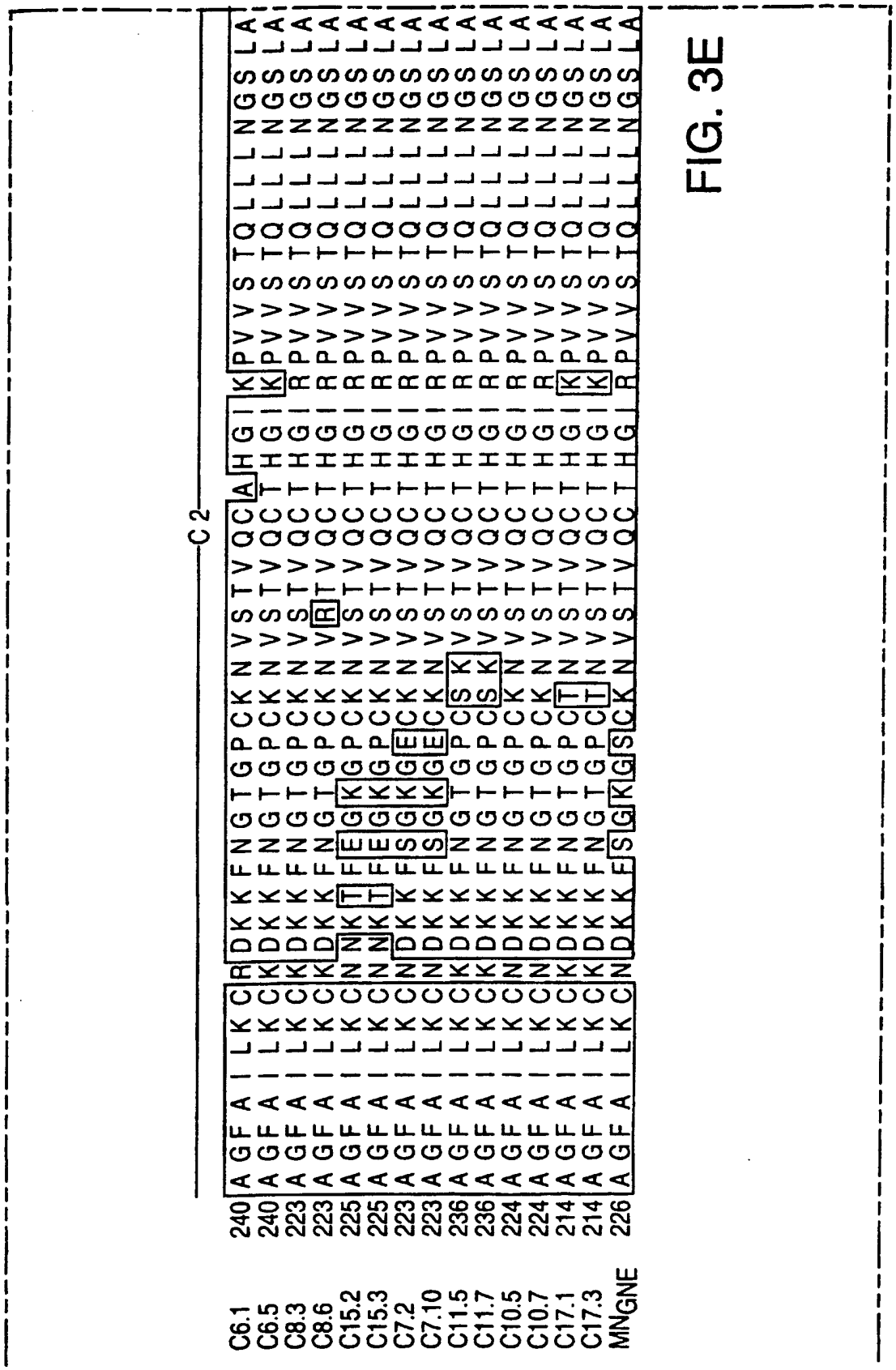
C2
240 A G F A I L K C R D K K F N G T G P C K N V S T V Q C A H G I K P V V S T Q L L L N G S L A
240 A G F A I L K C K D K K F N G T G P C K N V S T V Q C T H G I K P V V S T Q L L L N G S L A
223 A G F A I L K C K D K K F N G T G P C K N V S T V Q C T H G I R P V V S T Q L L L N G S L A
223 A G F A I L K C K D K K F N G T G P C K N V R T V Q C T H G I R P V V S T Q L L L N G S L A
225 A G F A I L K C N N K T F E G K G P C K N V S T V Q C T H G I R P V V S T Q L L L N G S L A
225 A G F A I L K C N N K T F E G K G P C K N V S T V Q C T H G I R P V V S T Q L L L N G S L A
223 A G F A I L K C N D K K F S G K G E C K N V S T V Q C T H G I R P V V S T Q L L L N G S L A
223 A G F A I L K C N D K K F S G K G E C K N V S T V Q C T H G I R P V V S T Q L L L N G S L A
236 A G F A I L K C K D K K F N G T G P C S K V S T V Q C T H G I R P V V S T Q L L L N G S L A
236 A G F A I L K C K D K K F N G T G P C S K V S T V Q C T H G I R P V V S T Q L L L N G S L A
224 A G F A I L K C N D K K F N G T G P C K N V S T V Q C T H G I R P V V S T Q L L L N G S L A
224 A G F A I L K C N D K K F N G T G P C K T N V S T V Q C T H G I R P V V S T Q L L L N G S L A
214 A G F A I L K C K D K K F N G T G P C T N V S T V Q C T H G I K P V V S T Q L L L N G S L A
214 A G F A I L K C K D K K F N G T G P C T N V S T V Q C T H G I K P V V S T Q L L L N G S L A
226 A G F A I L K C N D K K F S G K G P C K N V S T V Q C T H G I R P V V S T Q L L L N G S L A
C6.1
C6.5
C8.3
C8.6
C15.2
C15.3
C7.2
C7.10
C11.5
C11.7
C10.5
C10.7
C17.1
C17.3
MNGNE

FIG. 3E

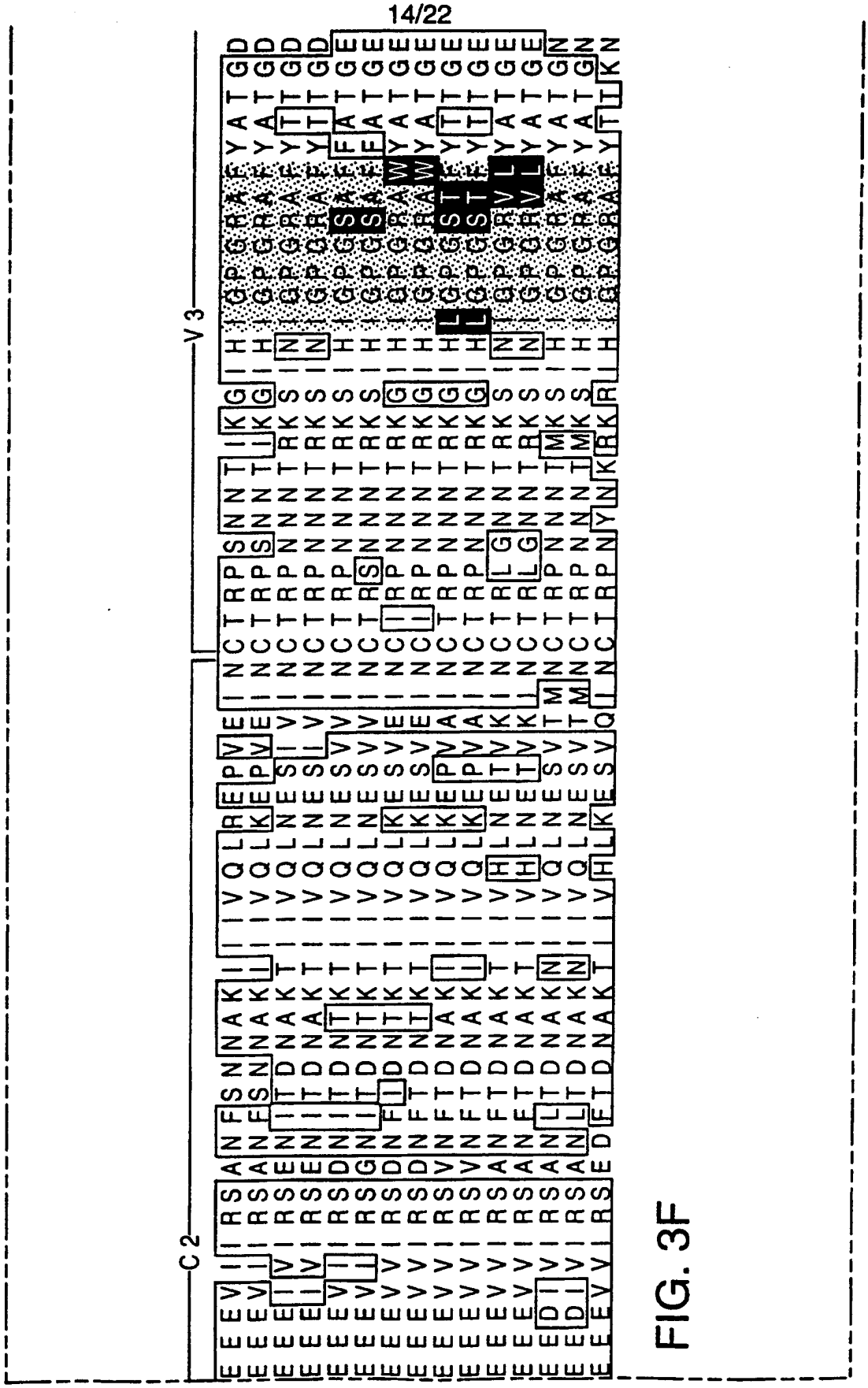

FIG. 3F

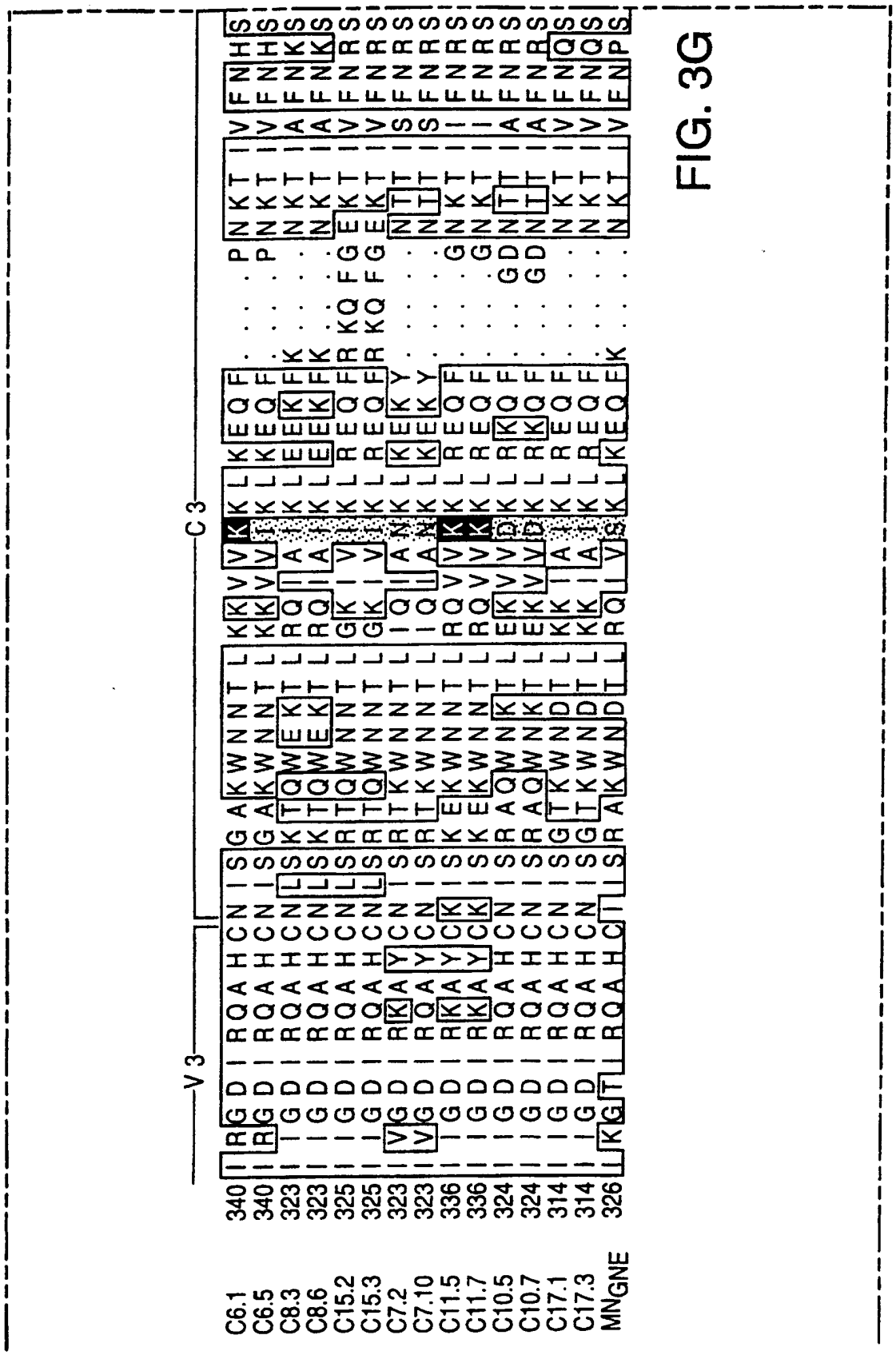
V3
C3
C6.1
C6.5
C8.3
C8.6
C15.2
C15.3
C7.2
C7.10
C11.5
C11.7
C10.5
C10.7
C17.1
C17.3
MNGNE

FIG. 3G

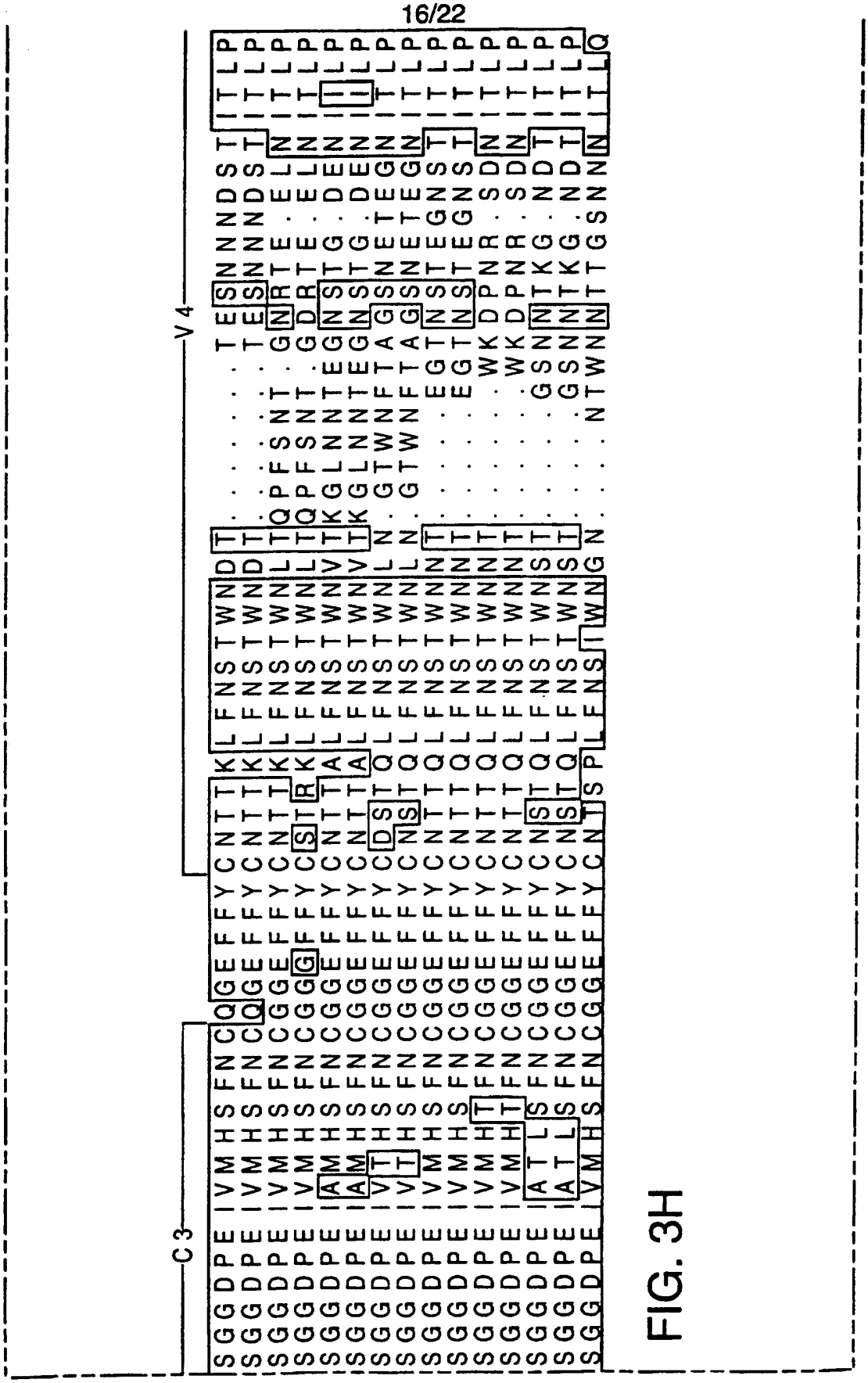

FIG. 3H

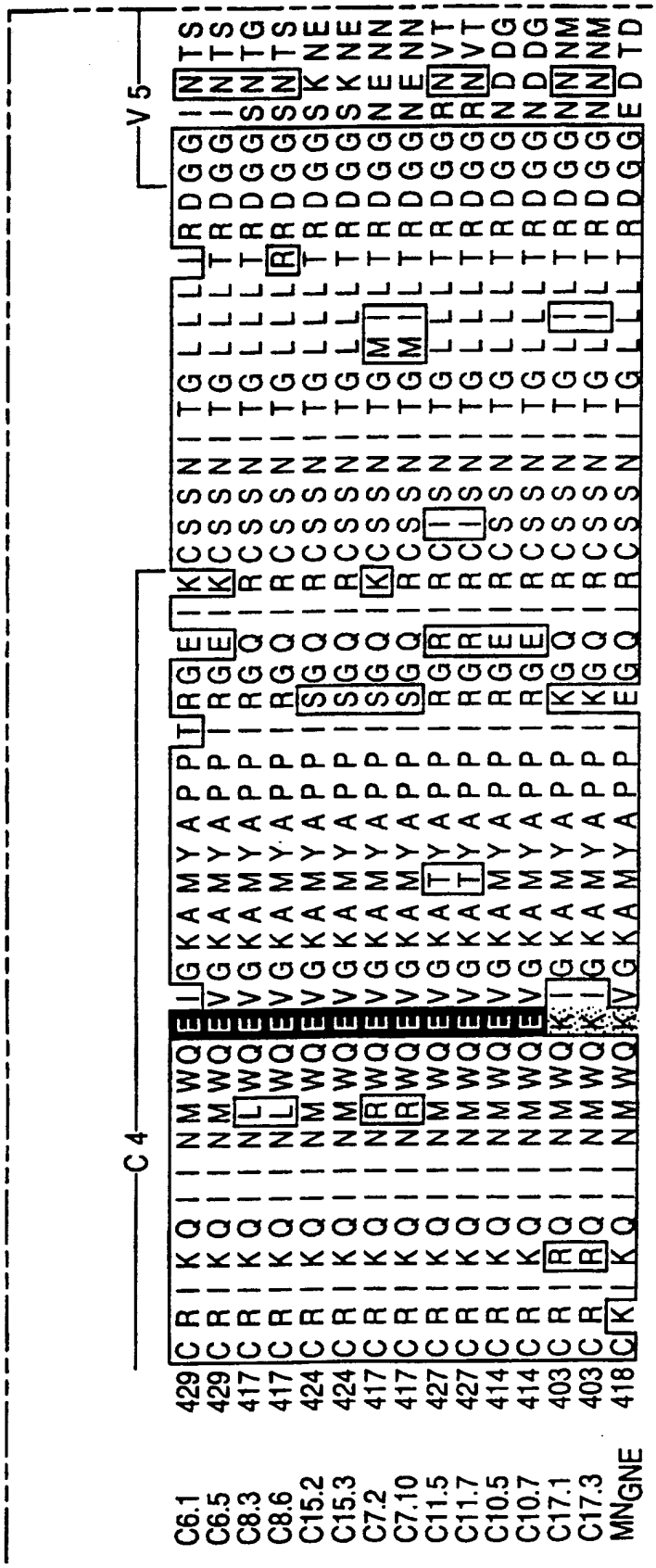
V5
C4
C6.1
C6.5
C8.3
C8.6
C15.2
C15.3
C7.2
C7.10
C11.5
C11.7
C10.5
C10.7
C17.1
C17.3
MNGNE

FIG. 3I

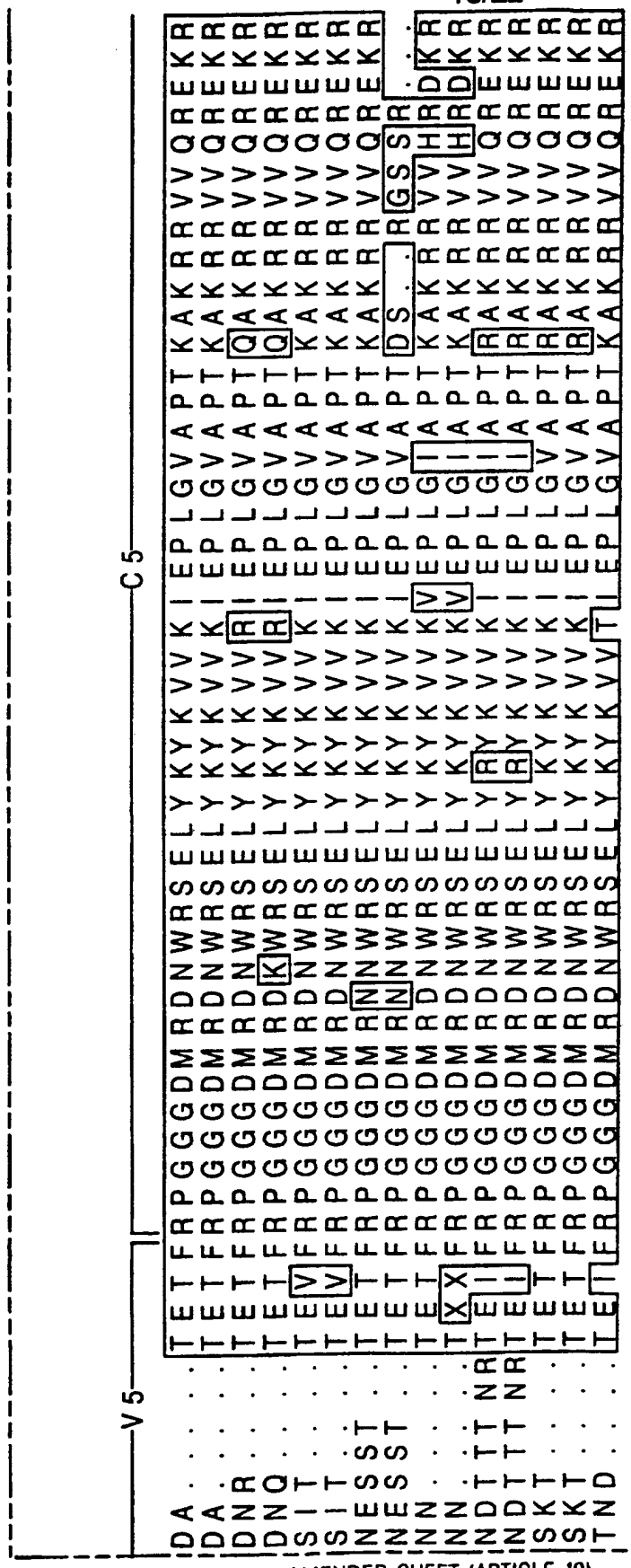

FIG. 3A	FIG. 3B			
FIG. 3C	FIG. 3D			
FIG. 3E	FIG. 3F			
FIG. 3G	FIG. 3H			
FIG. 3I	FIG. 3J			

FIG. 3

FIG. 3J

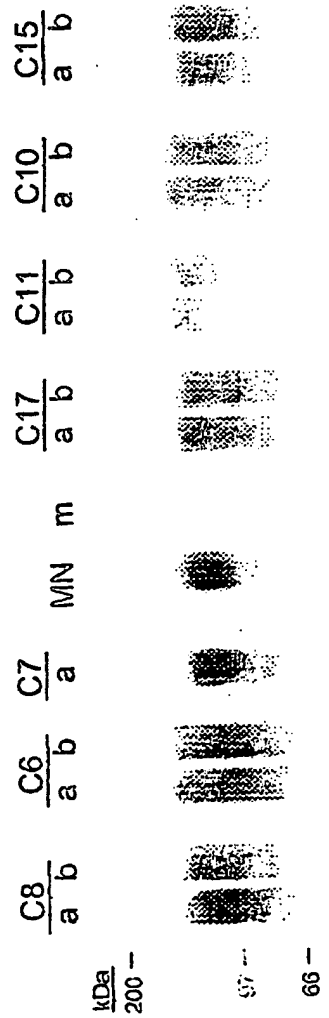

Fig. 5

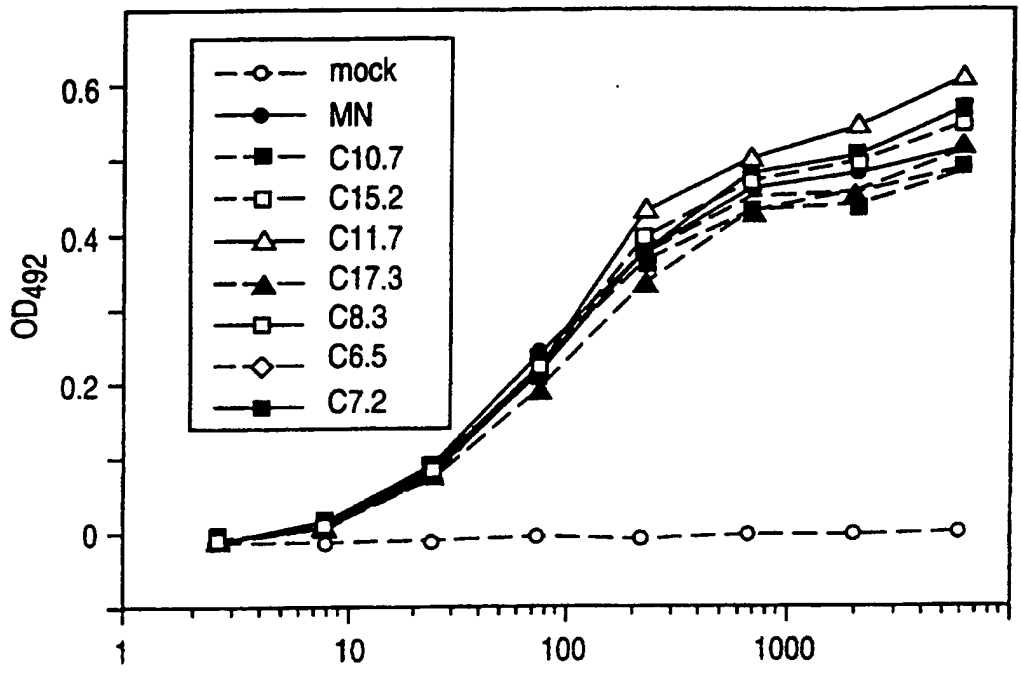
mock
MN
C10.7
C15.2
C11.7
C17.3
C8.3
C6.5
C7.2
0.6
0.4
0.2
0
OD492
1
10
100
1000
MAb (ng/ml)

FIG. 5A

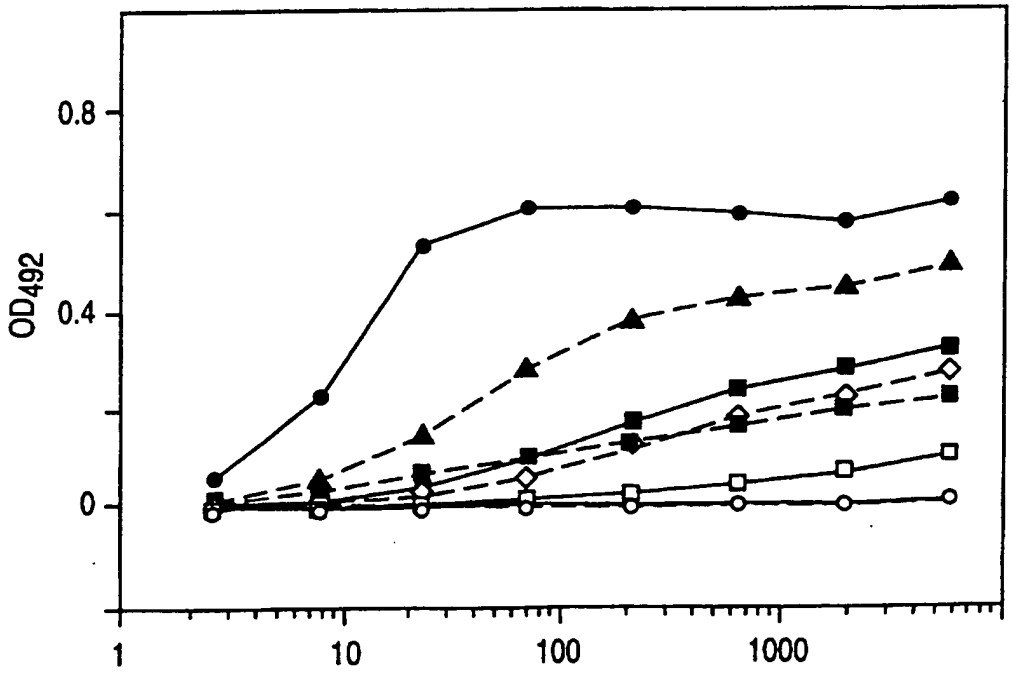
0.8
0.4
0
OD492
1
10
100
1000
MAb (ng/ml)

FIG. 5B

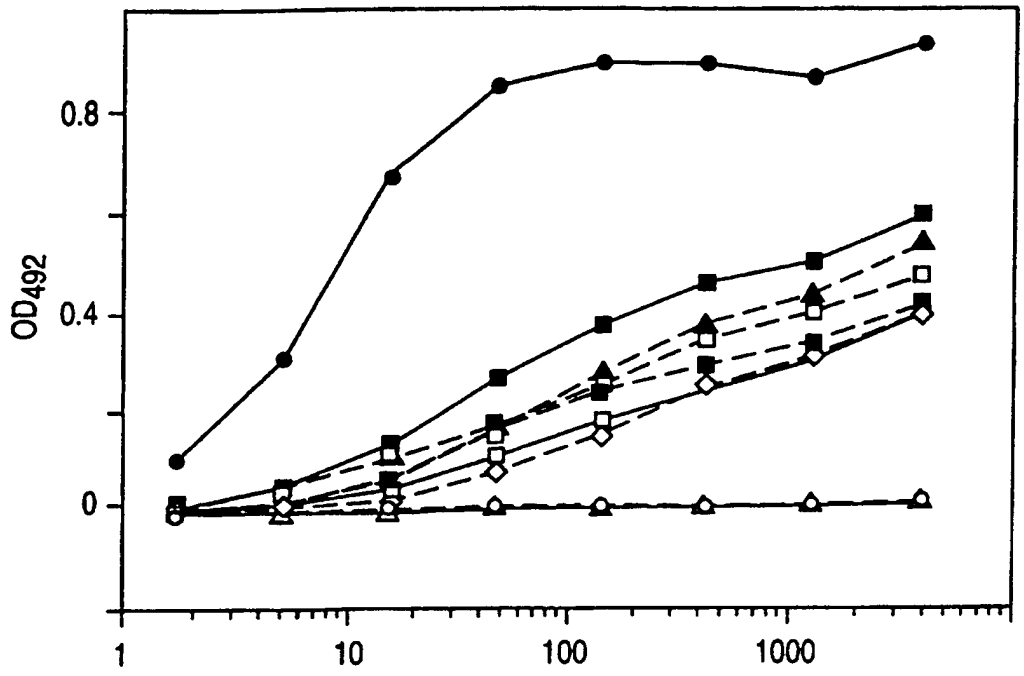
0.8
0.4
0
OD_{492}
1
10
100
1000
MAb (ng/ml)

FIG. 5C

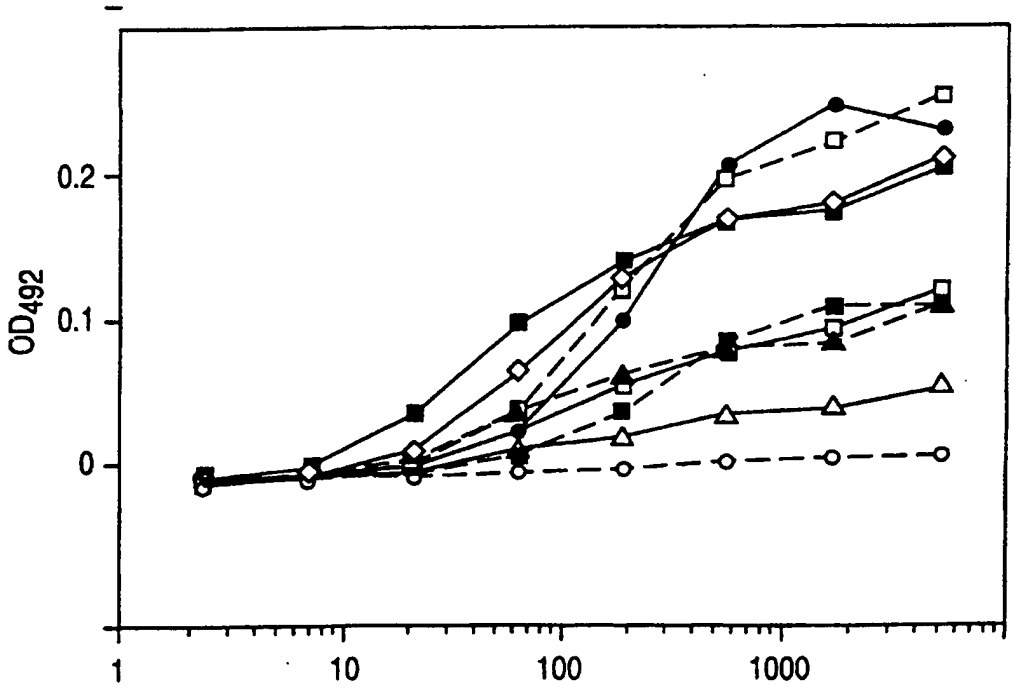
0.2
0.1
0
OD_{492}
1
10
100
1000
MAb (ng/ml)

FIG. 5D

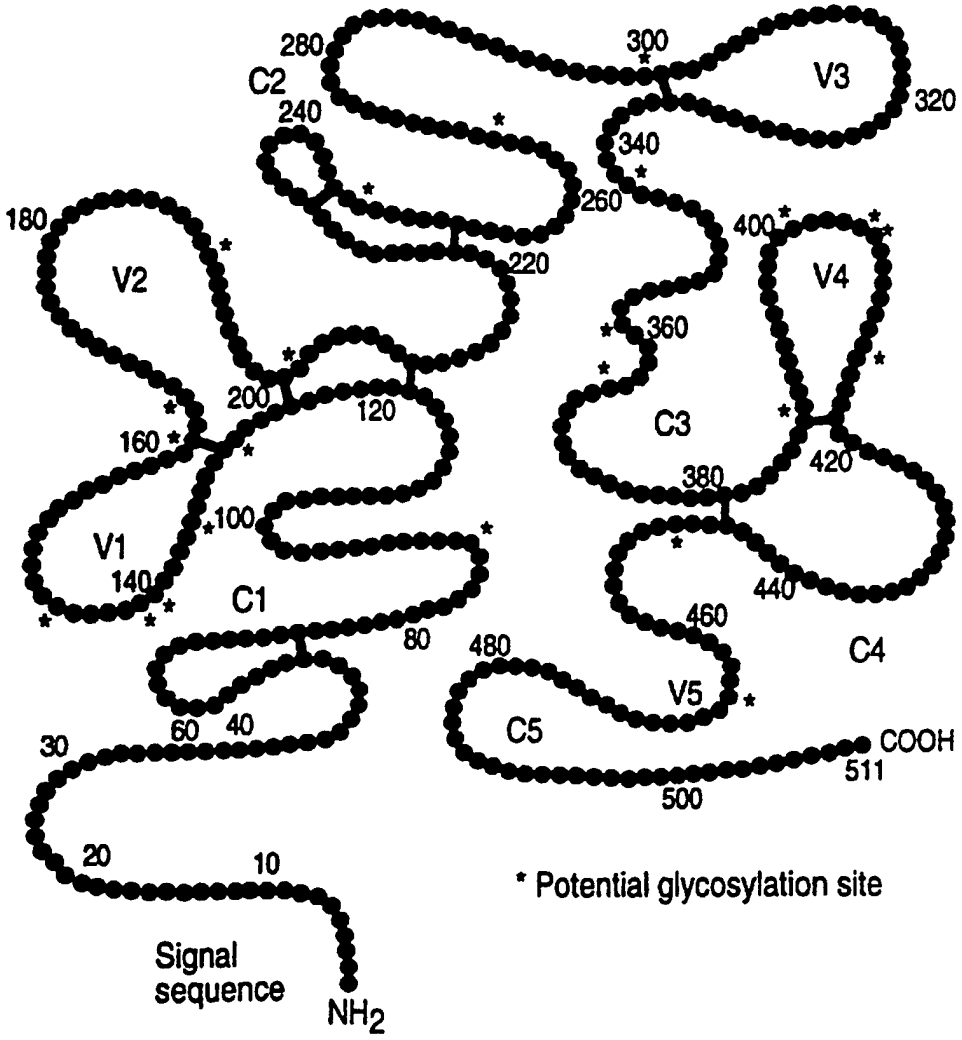
280
300
C2
V3
320
240
340
260
180
400
V2
220
V4
360
200
120
C3
160
420
380
100
V1
140
C1
440
460
80
480
C4
V5
60
40
C5
30
COOH
511
500
20
10
* Potential glycosylation site
Signal sequence
NH2

FIG. 6

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 97/09690

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/49 C07K14/16 A61K39/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 28929 A (GENETECH, INC.) 22 December 1994 see page 56 SEQ. ID. NO. 25. see page 50, line 14 - line 31 ---	1-18, 20-25
X	P.W. BERMAN ET AL.: "Genetic and immunologic characterization of viruses infecting MN-rgp120 vaccinated volunteers" ONE WORLD, ONE HOPE: XI INTERNATIONAL CONFERENCE ON AIDS, vol. 10, no. supplement 3, 7 - 12 July 1996, VANCOUVER, CANADA, page 10 XP002045307 See "Methods" in Abstract Mo.A.285 --- -/--	1,5,6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
30 October 1997	26 -11- 1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cupido, M

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/09690

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	M.J. MCELRATH ET AL.: "Human immunodeficiency virus type 1 infection despite prior immunization with a recombinant envelope vaccine regimen" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, no. 9, 30 April 1996, WASHINGTON US, pages 3972-3977, XP002045308 see page 3976, last paragraph; figure 1 ---	19
T	P.W. BERMAN ET AL.: "Genetic and immunologic characterization of viruses infecting MN-rgp120-vaccinated volunteers " THE JOURNAL OF INFECTIOUS DISEASES, vol. 176, no. 2, August 1997, pages 384-397, XP002045309 see the whole document -----	1-25

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 97/09690

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0708659 A	01-05-96